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| 14. ABSTRACT Many of the neuropsychological changes reported with PD are not typically seen early in the disease. One possible action of dopamine on the cerebral cortex is that of influencing activation within semantic networks. Thus, the goal of this project has been to study the semantic organization of verbal information in PD patients and matched controls, and determine the influence of dopamine on these cognitive processes. Data collected in our healthy subjects on the research task confirm our expectations that semantic processing can occur along a continuous gradient. Our preliminary data indicate that, when taking prescribed dopaminergic medication, our PD subjects demonstrate semantic processing that is similar to that of our control subjects. However, after an approximately 12-hour medication abstinence period, our PD subjects rated all semantically-associated stimuli as less similar than did controls. These results tentatively indicate that, as hypothesized, dopamine is involved in the mediation of neural activity. | | | | | |
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Introduction

Patients do not typically develop Parkinson's Disease (PD) until they lose approximately 70% of their dopaminergic neurons. This neural degenerative disorder typically induces motor deficits, but it is possible that subtle cognitive symptoms may precede the onset of the motor symptoms. In addition, screening for cognitive symptoms may be logistically easier than screening for motor deficits. However, it remains unclear as to what the early cognitive symptoms might be. There have been many excellent neuropsychological studies of patients with PD. These studies have revealed that patients with PD do have neuropsychological defects such as visuospatial disorders and evidence of frontal subcortical dysfunction. However, many of the neuropsychological changes reported with PD are not typically seen early in the disease and they are not seen in all subjects. Therefore, there is a need to develop new cognitive tests of PD that precede the motor symptoms, are easy to administer and are valid early predictors. In our research proposal we plan to develop cognitive tests that may be valid and reliable indicators of impending PD. In order to develop cognitive tests that predict the onset of the motor deficits associated with Parkinson's disease it is important to understand the effect of the dopaminergic system on the cerebral cortex. One possible action of dopamine on the cerebral cortex is that it increases the signal to noise ratio. Changing this ratio may influence activation of the semantic networks. One means of examining the activation patterns of semantic networks is to assess lexical priming. If cortical levels of dopamine influences priming, one would expect that patients with PD with a dopamine deficiency to have stronger priming for indirect words than would controls. In addition, the direct relationship may also be weakened in patients with PD. In this study, we will attempt to learn if patients with PD, when compared to control subjects, prime differently. We also plan to learn if PD performance is different when they are on and off L-dopa. We will further assess relationships in the semantic net by having experimental and control subjects judge the relatedness of words. To test self activation of the semantic net, we will assess word generation in these subjects. We will also study PD patients and matched controls ability to inhibit the semantic net through their ability to complete sentences with unrelated words and generate unrelated words. Further, we will induce dopamine blockade using haloperidol in normal subjects, and test these subjects for changes in the function of their semantic network using the same tasks discussed above. As agreed upon with the funding agency, we will not initiate the dopamine blockade component of this study until after we have had a chance to fully evaluate the findings in the PD and similarly-aged control subjects. Finally, as stated in our Revised Statement of Work, we will evaluate and validate a revised version of the computerized semantics judgments task that is to be incorporated into the Automated Neuropsychological Assessment Metric (ANAM), as well as assess the relationship between semantic processing and frontal-executive functions using select subtests from the ANAM.

Body

We spent the first year of this grant in test development. This activity involved reviewing the current literature on verbal and semantic priming, and deriving appropriate tasks to address our hypotheses regarding semantic priming in PD. This review culminated in a selection of word pairs and word primes (Balota & Lorch, 1986, Bennett & McEvoy, in press, McNamara, 1992, McRae & Boisvert, 1998, Nelson et al., 1998, Shelton & Martin, 1992) for our relatedness judgment task and word generation tasks, which have some normative basis. These stimuli also allowed us to assess differences in strength of verbal relatedness, and differences in strength of verbal mediation. The tests that were developed include a word priming task which requires the subject to identify a stimulus as either a real word or a nonsense word. Another test involves having the subject determine the degree of relatedness between two words that have been pre-selected based on normative-based judgments of relatedness. A third task involves having the subject generate a single word to a stimulus cue that has been pre-selected based on a normative-based assessment of semantic activation of that cue. This review also provided us with a list of semantic categories that have normative data for our word generation tasks (Battig & Montague, 1969). The tests derived from this list of categories require the subject to generate exemplars that either match or do not match the target category. As part of this process, we developed computer programs for the administration of some of these tasks that will facilitate data collection and analysis. We also developed referral sources from which to recruit subjects for this study. We initiated data collection at the end of the first year of this grant.

We spent the second year of this study with subject recruitment and data collection. Subject recruitment has involved daily patient screening in the Neurology Clinics of both Shands Hospital at the University of Florida, and the Malcolm Randal VAMC. We also initiated contacts with the Neurology Clinics at the Lake City VAMC and the University of Florida Health Science Center at Jacksonville for subject recruitment through these respective locations. This external recruitment was approved by the University of Florida Health Science Center Institutional Review Board (IRB). Data was collected on 17 volunteers by the end of the second year of this protocol, including seven men and three women with Parkinson's Disease, and three men and four women as control subjects. However, we had some difficulty recruiting appropriate control subjects, and having Parkinsonian patients return "off" their PD medications, thus resulting in incomplete data. Consequently, there was no reportable data at the end of the second year of this project.

The third year of this project was spent with subject recruitment and data collection. Data was collected on nine additional subjects during this last period, including three men with PD, three women with PD, and three female control subjects. Preliminary analyses reveal that control subjects show the typical facilitation in reaction time (e.g., priming) for strongly related associations, yet an increase in reaction time responding to weakly related associations (e.g., negative priming), indicating that concepts that are weakly related appear to require more time in processing the nature of that semantic relationship. The PD subjects showed a similar, albeit diminished, pattern of priming when not taking their prescribed dopaminergic medications. However, these same PD subjects showed priming for the weakly related associations when taking their prescribed Parkinsonian medications. Thus, exogenous dopamine in PD subjects appears to reverse the negative priming effect associated with weakly associated concepts. A similar pattern of responding was seen in the PD subjects on the relatedness judgment task. The time to process the relationship between two indirectly associated words is much shorter when taking dopaminergic medication than when not taking these medications. Thus, exogenous dopamine in individuals with PD appears to enhance the semantic processing of distantly related concepts. Taken together, these results suggest that dopamine affects semantic processing in a curvilinear manner. Normal dopamine function, as seen in the control subjects, facilitates the semantic processing in strong conceptual relationships and interferes with semantic processing in weak and/or indirect relationships. Severe dopamine depletion, as seen in the PD subjects when not taking their dopaminergic medication results in a similar, but diminished pattern of semantic processing. In contrast, PD subjects show enhanced semantic processing of weak and indirectly related concepts when taking their prescribed medications. We continued to actively recruit subjects and collect data during the remaining time in this project.

The fourth year of this study was spent recruiting and testing subjects, and recording their data. We were granted a two-year extension of this study from the Department of Defense to continue pursuing this line of research. As such, we submitted the report for the fourth year as an Annual Report rather than as the Final Report, and we continued to actively recruit subjects and collect data during the remaining time in this project.

We spent the fifth, sixth and seventh years of this study recruiting and testing subjects, and recording their data. Data on the Relatedness Judgments Task was collected from a total of 60 young adults, 33 older adults, and 29 adults with Parkinson's Disease. Preliminary results in our healthy subjects indicate that, as expected, semantic processing can occur along a continuous gradient (Crucian et al., 2004; see attached). These data show that, as predicted, strongly associated word-pairs are rated as significantly more similar in meaning than moderately associated word-pairs, weakly associated word-pairs or mediated word-pairs. In fact, the ratings of each word-pair associate group were significantly distinguishable from the other groups (see Table). Thus, consistent with our hypothesis, semantic processing can occur along a continuous gradient in evaluating the conceptual relationship between different words in healthy normal individuals. Preliminary findings also indicate that subjects with Parkinson's Disease who were off their L-dopa medication, when tested on the Judgment Relatedness Test which requires subjects to determine the degree of semantic relatedness between two verbal concepts, showed significant attenuation in their evaluations of distantly-related concepts. That is, compared to the control subjects similar in age and education, PD subjects rated the associated word-pairs as less similar when "off" their dopaminergic medications (45.40 ± 3.40 versus 55.27 ± 3.29) than when "on" these medications (47.59 ± 3.33). No effect for semantic level was found, indicating that dopamine depletion impacted semantic processing globally rather than at different levels the semantic net. These preliminary findings are consistent with the hypotheses of this study that dopamine is directly involved in the modulation of neural activity within semantic networks. During this fifth year of the study, we also initiated the work necessary to integrate the Relatedness Judgments Task into the Automated Neuropsychological Assessment Metric battery (ANAM), as requested by the Department of Defense and stated in our approved Revised Statement of Work. As such, we began collecting data on the ANAM version of the Judgment Relatedness Test in order to corroborate this version with the original version of the task. In addition and as stated in our approved Revised Statement of Work, we also begun administering measures of executive function from the ANAM (e.g., Tower of Hanoi Task) as part of our test battery in order to further elucidate the nature of semantic processing and the influence of dopamine on these cognitive functions.

During the past period (i.e., the eighth year) of this project, we have continued to collect data for this study. To date, data on the Relatedness Judgments Test has been collected on a total of 60 young adults, 38 older adults, and 41 individuals with Parkinson's Disease. Data is also currently being collected on the ANAM version of the Relatedness Judgments Test as well as the ANAM Tower of Hanoi Test. These data are currently being compiled and analyzed, and results are not yet available. These results will be presented upon completion of the data analysis.

We have also presented results from auxiliary studies associated with this project. One recent manuscript has been submitted reporting our findings on memory deficits in individuals with PD. Several posters have also been presented at the annual conference for the International Neuropsychological Society. These posters reflect studies looking at deficits in visual-spatial ability, memory, and executive functions in our subjects with Parkinson's Disease.

We intend to continue actively analyzing this data through the complete assessment of our hypotheses. These results will be presented as these analyses are completed.

Table: Relatedness Judgments Composite Scores

| Test Version | Strongly | Moderately | Weakly | 1-Step Med. | 2-Step Med. |
|--------------|---------------|---------------|---------------|---------------|---------------|
| | Associated | Associated | Associated | Associated | Associated |
| A | 73.42 (15.27) | 68.11 (12.07) | 50.12 (12.55) | 41.03 (13.09) | 11.94 (10.15) |
| B | 76.49 (11.66) | 72.97 (12.64) | 55.38 (14.33) | 44.77 (15.75) | 25.72 (11.48) |

Key Research Accomplishments

We have established a test of semantic processing that involves a continuous scale of measurement rather than a discrete or dichotomous measurement scale. This new test will allow for a more sensitive assessment of semantic processing. Preliminary analyses at this time indicate that this new test is reasonably reliable and stable

over time. We have also incorporated this new test of semantic processing into the computerized testing format of the Automated Neuropsychological Assessment Metric (ANAM). In addition to work directly on this DoD-funded project, we have been actively pursuing parallel lines of research on cognitive dysfunction in Parkinson's Disease. This parallel research resulted in a recent publication in which we presented data showing visual-spatial mental rotation deficits in individuals with Parkinson's Disease, particularly men with PD, compared to control subjects similar in age and education (Crucian et al., 2003; see appendices).

Reportable Outcomes

Barrett, A.M., Crucian, G.P., Schwartz, R.L., Nallamshetty, H. and Heilman, K.M. Seeing trees but not the forest, limited perception of large configurations in Parkinson's Disease. *Neurology* 56:724-729, 2001.

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Crucian, G.P., Barrett, A.M., Schwartz, R.L., Bowers, D., Triggs, W.J., Friedman, W., Heilman, K.M. Cognitive and vestibulo-proprioceptive components of spatial ability in Parkinson's disease, *Neuropsychologia* 38 (6) 757-67, 2000.

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Crucian, G.P., Burks, D., Mielke, J., Shenal, B., Rhodes, R., Grande, L., Womack, K., Riestra, A., Okun, M.S., Bowers, D., & Heilman, K.M. Memory in Parkinson's Disease: A step-wise analysis. Poster presented at the 32nd annual meeting of the International Neuropsychological Society, Baltimore, MD, February, **2004**. (Journal of the International Neuropsychological Society, 10(S1), 66.)

Crucian, G.P., Tulman, J., Sell, S., Grande, L.J., Burks, D.W., Shenal, B.V., Rhodes, R., Mielke, J.B., Riestra, A., Womack, K., Okun, M.S., Reeves, D.L., Crosson, B., & Heilman, K.M. The relatedness judgments task: A test of semantic association. Poster presented at the 32nd annual meeting of the International Neuropsychological Society, Baltimore, MD, February, 2004. (Journal of the International Neuropsychological Society, 10(S1), 108).

Crucian, G.P., Barrett, A.M., Burks, D.W., Riestra, A., Roth, H.L., Schwartz, R.L., Triggs, W.J., Bowers, D., Friedman, W., Greer, M., & Heilman, K.M. (2003). Object spatial orientation in parkinson's disease. Journal of the International Neuropsychological Society, 9, 1078-1087.

Drago, V., Foster, P.S., **Crucian, G.P.**, & Heilman, K.M. Cognitive festination and impersistence in parkinson's disease. Poster presented at the 34th annual meeting of the International Neuropsychological Society, Boston, MA, February, **2006**. (Journal of the International Neuropsychological Society, 12 (S1), 170)

Foster, P.S., Drago, V., Rhodes, R., Crucian, G.P., & Heilman, K.M. Neuropsychological functioning in Parkinson's disease: The effects of asymmetrical symptom presentation and anxiety. Submitted for presentation to the 33rd annual meeting of the International Neuropsychological Society.

Foster, P.S., Drago, V., Rhodes, R., Crucian, G.P., & Heilman, K.M. Relationships between verbal and nonverbal memory and the laterality of Parkinsonian signs. Submitted for presentation to the 33rd annual meeting of the International Neuropsychological Society.

Foster, P.S., Rhodes, R.D., Lohse, B., Shenal, B., Crucian, G.P. & Heilman, K.M. Learning in Alzheimer's and Parkinson's disease. Submitted for presentation to the 33rd annual meeting of the International Neuropsychological Society.

Foster, P.S., Drago, V., Rhodes, R., Crucian, G.P., & Heilman, K.M. The effects of mental processing speed on immediate and delayed recognition in Parkinson's disease. Submitted for presentation to the 33rd annual meeting of the International Neuropsychological Society.

Grande LJ, Crosson B, Heilman KM, Bauer RM, Kilduff P, McGlinchey RE (2006) Visual selective attention in Parkinson's disease: dissociation of exogenous and endogenous inhibition. *Neuropsychology*. 20(3):370-82.

Grande, L., Crucian, G., & Heilman, K.M. Semantic priming in patients with parkinson's disease on and off dopamine medication. Poster presented at the 30th annual meeting of the International Neuropsychological

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Conclusions

The results to date indicate that 1.) semantic processing can reliably occur along a continuous gradient, and 2.) individuals with PD, when "off" their dopaminergic medications, show significant attenuation in their semantic processing of word-pairs compared to healthy control subjects similar in age and education. These results are consistent with our hypotheses that dopamine is involved in the modulation of activation within the semantic networks. These results suggest that catecholamines (e.g., dopamine) are involved, to some extent, in the evaluation and comparison in meanings of different verbal concepts.

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Submitted Abstract

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Abstract

TITLE:

The Relatedness Judgments Task: A Test of Semantic Association

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ABSTRACT BODY:

Lexical priming and word association tasks provide a measure of semantic organization/processing. In lexical priming, a semantic relationship with the cue facilitates recognition of the target word, suggesting cues increase activation within that semantic network. In word association tasks, subjects say the first word that comes to mind in response to a cue, suggesting a conceptual/associative relationship between words. Whereas both tasks presume existence of a semantic relationship between words, neither takes into account degree of conceptual/associative relationship in semantic processing. Thus, these semantic processing tasks may not reflect the full extent of semantic associations being generated. In this study, we report findings of a semantic processing measure currently under development. In this task, subjects are presented with word pairs and asked to rate degree of "relatedness" using a Likert scale. Strength of relationship between words was manipulated, deriving 3 groups (strong, moderate, weak) based on word association normative data. Two groups of mediated word pairs (the relationship between words is "mediated" by one or two words) were also included to broaden the range of semantic processing being assessed. Results from a group of young (14 men, 16 women; mean age = 20.8 years) and older adults (7 men, 9 women; mean age = 68.5 years) reveal the categories of word pairs are reliably differentiated as expected. That is, strongly-associated word pairs are rated as more related than weakly-associated or mediated word pairs. Findings confirm the premise that semantic processing involves assessment of degree of similarity between two concepts. Results suggest that assessment of degree of conceptual relationship may be an important consideration in evaluating semantic processing. This measure may have utility in assessing neurological conditions such as Alzheimer's and Parkinson's Disease where there might be alterations in semantic representations.

Abstracts Presented at the Thirtieth Annual International Neuropsychological Society Conference

February 13–16, 2002 Toronto, Canada

L. GRANDE, G. CRUCIAN, & K.M. HEILMAN. Semantic Priming in Patients with Parkinson's Disease On and Off Dopamine Medication.

Studies investigating cognition in healthy individuals have indicated a role of dopamine in the modulation of the signal-to-noise-ratio within semantic memory (Newman et al., 1984; Kischka et al., 1996). This study investigated dopamine's effects on semantic networks by testing priming in participants with idiopathic Parkinson's disease (PD) ($n = 10$) and healthy controls (HC) ($n = 8$). Each participant completed a semantic priming-lexical decision experiment involving 3 levels of semantic association: high prototypicality (e.g., gem–ruby), low prototypicality (e.g., gem–quartz), and unrelated (e.g., gem–shoe). Each PD participant completed the experiments both on and off their dopamine medication. For the HC group, comparison of response latencies across conditions revealed priming for targets of high prototypicality and no priming for targets of low prototypicality. In contrast, the PD group on medications demonstrated an overall pattern of semantic priming, but no effect of prototypicality. Additionally, the PD group off medications did not demonstrate an effect of either prototypicality or semantic relatedness. These results appear to support the hypothesis that dopamine may focus semantic activation. Correspondence: *Laura Grande, GRECC (182 JP) VA Boston Healthcare System, 150 South Huntington Ave., Boston, MA 02130. grande@nersp.ncrdc.ufl.edu*

Mental object rotation in Parkinson's disease

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Abstract

Deficits in visual-spatial ability can be associated with Parkinson's disease (PD), and there are several possible reasons for these deficits. Dysfunction in frontal–striatal and/or frontal–parietal systems, associated with dopamine deficiency, might disrupt cognitive processes either supporting (e.g., working memory) or subserving visual-spatial computations. The goal of this study was to assess visual–spatial orientation ability in individuals with PD using the Mental Rotations Test (MRT), along with other measures of cognitive function. Non-demented men with PD were significantly less accurate on this test than matched control men. In contrast, women with PD performed similarly to matched control women, but both groups of women did not perform much better than chance. Further, mental rotation accuracy in men correlated with their executive skills involving mental processing and psychomotor speed. In women with PD, however, mental rotation accuracy correlated negatively with verbal memory, indicating that higher mental rotation performance was associated with lower ability in verbal memory. These results indicate that PD is associated with visual–spatial orientation deficits in men. Women with PD and control women both performed poorly on the MRT, possibly reflecting a floor effect. Although men and women with PD appear to engage different cognitive processes in this task, the reason for the sex difference remains to be elucidated. (*JINS*, 2003, **9**, 1078–1087.)

Keywords: Parkinson's disease, Visual–spatial orientation, Mental rotation, Gender differences

INTRODUCTION

Parkinson's disease (PD) has been associated with deficits on visual–spatial tasks (Cummings & Huber, 1992; Growdon & Corkin, 1986; Stern & Mayeux, 1986). However, a recent meta-analysis of this literature (Waterfall & Crowe, 1995) suggested that visual–spatial deficits in PD are not universal because deficits are seen primarily on multifactorial visual–spatial tasks (e.g., Raven's Progressive Matrices) but not more unifactorial measures of visual–spatial ability (e.g., Judgment of Line Orientation, Embedded Figures Test). This conclusion was similar to those of Lazaruk (1994). Thus, the relationship between visual–spatial ability and PD is not clear.

One theory of cognitive dysfunction in PD suggests that these deficits are related to disturbance in the frontal–basal ganglia neural circuits important in executive functions such as attention and concentration, sequencing, working memory, and set-shifting (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995). This executive dysfunction theory was supported by a study that found a significant relationship between executive dysfunction and visual–spatial deficits in individuals with PD (Bondi et al., 1993). In a group of 19 individuals with mild to moderate PD, these investigators found that statistically controlling for the deficits in executive skills (e.g., Wisconsin Card Sorting Test, California Sorting Test) through an analysis of covariance eliminated the visual–spatial deficits (e.g., WAIS–R Picture Arrangement, Benton Facial Discrimination Test), but statistically controlling for the visual–spatial deficits did not alter the abnormal measures of executive function.

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In contrast, Cronin-Golomb and Braun (1997) provide evidence for a visual–spatial deficit in PD that is independent of executive skills. In a group of 50 non-demented, non-depressed, individuals with mild to moderate PD, these investigators found deficiencies on Subtest A of Raven’s Colored Progressive Matrices (RCPM) when compared to matched control subjects. Because Subtest A of the RCPM has a greater visual–spatial component than the remaining portions of the RCPM, and because the PD subjects’ RCPM-A performance was related to other measures of visual–spatial ability (e.g., Luria’s Mental Rotation Test, Standardized Road-Map Test of Direction Sense), but not measures of executive function (e.g., Stroop test, WAIS–R Picture Arrangement), they concluded that PD was associated with a visual–spatial problem-solving deficit.

Visual–spatial abilities as usually tested involve several distinct cognitive processes (Ekstrom et al., 1976), and the visual–spatial tasks used in the studies reviewed above are generally considered to be complex, involving multiple cognitive processes. Therefore, a significant problem with this literature is the visual–spatial tasks used and their dependence on other cognitive processes (Waterfall & Crowe, 1995). Mental rotation ability is correlated with other visual–spatial skills (Bryden, 1982; McGee, 1979; Stumpf & Eliot, 1999) and may offer a way of more directly examining this issue. However, mental rotation data in PD is also variable. Previous studies have found no significant differences in accuracy of mental rotation between individuals with Parkinson’s disease and control subjects (Boller et al., 1984; Brown & Marsden, 1986; Goldenberg et al., 1986; Raskin et al., 1992; Smith et al., 1998; Taylor et al., 1986). One possible limitation of these negative studies, however, was the failure to use sensitive measures that limit verbal mediation and require both two- and three-dimensional rotations. For example, some studies (Boller et al., 1984; Brown & Marsden, 1986; Taylor et al., 1986) used tasks that are limited to two dimensions (e.g., letter rotation, map direction task) and could be verbally mediated. Other studies (Goldenberg et al., 1986; Raskin et al., 1992) used a manikin rotation task that can also be verbally mediated. However, a recent study using a tachistoscopic cube-figure presentation method similar to the mental rotation task of Shepard and Metzler (1971), which requires subjects to make same-different judgments when two objects are presented in different three-dimensional orientations, found that PD subjects were less accurate than control subjects in making “same” judgments (Lee et al., 1998). However, when compared to control subjects, these same PD subjects also had significantly faster response times when making “same” judgments, suggesting that the mental rotation deficit in these PD subjects might have been due to a speed–accuracy trade-off. Supporting this conclusion were the observations that slower response times for “different” judgments of three-dimensional stimuli, and “same” and “different” judgments of two-dimensional stimuli, were associated with normal accuracy. Thus, these findings do not differentiate whether these deficits in PD are due to problems in visual–spatial ability or deficiencies in psychomotor and mental processing speed which are common in PD. In addition, there was also no other testing to exclude the possible confound of an associated dementia.

Because it remains unclear if mental rotation deficits exist in non-demented individuals with Parkinson’s disease, we studied a population of non-demented subjects with PD using the Mental Rotations Test (MRT) which requires the participant to recognize a target stimulus in different two- and three-dimensional spatial orientations (Linn & Petersen, 1985; Shepard, 1978; Shepard & Metzler, 1971). We also examined these PD subjects’ performance on other tests of cognitive function, particularly executive skills, to ascertain the relationship between these other cognitive functions and mental rotation ability.

METHODS

Research Participants

Twenty-eight men and 23 women with PD were recruited from the Neurology and the Neurosurgery clinics at the University of Florida Health Science Center as experimental subjects for this study. Most of these volunteers were being evaluated for surgical treatment of their PD, whereas the remaining few were seen in the clinic for their periodic neurological evaluation. Hospital volunteers, as well as family members and friends who accompanied the PD patients to the clinic were recruited as controls (28 men and 28 women). Exclusionary criteria for enrollment in this study (experimental and control subjects) included use of the left hand for writing, a history of learning disabilities, a history of other or concurrent neurological disorders, and a previous history of major psychiatric disorder prior to PD onset.

The presence of dementia was assessed in 105 of 107 subjects with the Mini Mental Status Exam (MMSE; Folstein et al., 1975), with a cut-off criterion of 27/30. A higher than usual cut-off criterion was used in this study to minimize the likelihood of a confounding neurodegenerative disease other than PD being present (Malapani et al., 1994; Reed et al., 1997). Two female control subjects did not receive the MMSE because they were gainfully employed at the time of testing and dementia screening was deemed unnecessary. The motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elston, 1987) was administered to characterize the motor dysfunction of the PD subjects. The Parkinson's subjects were also screened for depression with the Geriatric Depression Scale (GDS; Yesavage et al., 1983). It should be noted that 9 PD subjects did not receive the GDS, and 2 PD subjects did not receive the UPDRS.

Demographic data for the respective groups are presented in Table 1. Please see Table 2 for the PD subjects' medications. There was no statistically significant difference in the numerical composition of the subject groups [$\chi^2 = 0.612$, $df = 1$, $N = 107$; n.s.]. There were no significant differences between PD patients and control subjects

Controls Males Females Demographics *M (SD)* *M (SD)*

Parkinson's Males Females *M (SD)* *M (SD)*

Age (yrs) 66.44 (9.11) 63.22 (8.82) 62.72 (7.67) 62.23 (9.67) Education (yrs) 14.32 (3.31) 13.86 (2.35) 14.75 (2.53) 13.39 (2.06) MMSE 29.04 (0.99) 29.46 (0.81) 29.00 (0.98) 28.78 (0.80) Duration (yrs) — — 11.68 (5.92) 10.15 (6.07) UPDRS-Motor — — 27.57 (11.03) 36.19 (15.12)

in age or education, and no difference between male and female PD subjects in disease duration. However, the female PD patients had significantly more motor symptoms than male Parkinson's patients on the UPDRS Motor Scale (Mann-Whitney $U = 189.50$, $p = .035$). These UPDRS scores place the males with PD generally in the mild to moderate range of motor impairment (approximating a Hoehn & Yahr, 1967, Stage III to Stage IV), and the female PD patients in the moderate range of impairment (approximating a Hoehn & Yahr, 1967, Stage IV). Based on results from the UPDRS Motor Scale, 15 Parkinson's subjects exhibited predominantly right-sided symptoms, 11 exhibited predominantly left-sided symptoms, and 23 subjects exhibited bilateral symptoms. Results from the UPDRS Motor Scale also indicated that 27 Parkinson's subjects exhibited predominantly rigid-akinetic symptoms, 9 exhibited predominantly tremor, and the symptom presentation of 13 Parkinson's subjects could not be differentiated, exhibiting both rigid-akinesia and tremor to a similar degree. Based on responses to the GDS, 21 PD subjects reported no consistent symp-

Table 2. Summary of medication status of PD subjects

| Type of medication | Number of subject |
|---|-------------------|
| Dopaminergic | 51 |
| Carbidopa–Levodopa | 49 |
| Selegiline | 9 |
| Amantadine | 5 |
| Ropinirole | 2 |
| Bromocriptine | 4 |
| Pergolide | 6 |
| Trihexyphenidyl (antispasmodic) | 4 |
| Benztropine (anticholinergic0antihistimine) | 1 |
| Pramipexole (dopamine agonist) | 1 |
| Tramadol (analgesic) | 1 |
| Benzodiazapine | |
| Lorazepam, Clonazepam, Temazepam | 19 |
| Clorazepate | 1 |
| Sleep Aids (Phenobarbitol, Zolpidem, Tartate) | 3 |
| Primidone | 2 |
| Antidepressants (doxepin, sertraline, paroxetine) | 11 |

toms of depression, 16 PD subjects reported symptoms of mild depression, and 5 subjects reported symptoms of moderate to severe depression (see Spreen & Strauss, 1998 for scoring criteria).

Parkinsonian patients also received neuropsychological testing as part of their clinical evaluation. These neuropsychological tests were selected to assess for current level of general intellectual skills, memory for verbal and visual– spatial information, language, visual–spatial ability, and executive functions involving speeded mental processing and set-shifting. Tests included the Information, Similarities, Digit Span, Digit Symbol, and Block Design subtests from the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981), Logical Memory I and II and Visual Reproduction I and II from the Wechsler Memory Scale–Revised (Wechsler, 1987), California Verbal Learning Test (CVLT; Delis et al., 1987), Boston Naming Test (BNT; Kaplan et al., 1983), Controlled Oral Word Associations (COWA; Spreen & Benton, 1977), Stroop Color Word Test (Golden, 1978), and the Trail Making Test (Trails; Reitan & Wolfson, 1985). These tests were administered and scored according to standardized instructions using normative data adjusted for age and education where available. Due to time constraints in the clinical evaluation, some of the PD subjects did not receive all of the tests (Table 3). Neuropsychological test results from the cognitive screening are also presented in Table 3. Review of Table 3 indicates that the level of cognitive functioning in this sample of Parkinsonian subjects is generally within normal limits (see Spreen & Strauss, 1998; Wechsler, 1981, 1987 for normative data), with no discrepancies between measures of crystallized knowledge (e.g., WAIS–R Information subtest) and verbal abstract reasoning (e.g., WAIS–R Similarities subtest). Performance on the WAIS–R Block Design, although variable, was within normal limits. These subjects also show no deficits in confrontation naming (e.g., Boston Naming Test), verbal fluency (e.g., COWA), or memory for either verbal or visual-spatial information (e.g., WMS–R, CVLT). Test results are noteworthy for some psychomotor slowing as seen on Trails B of the Trail Making Test. These test findings are generally consistent with the PD subjects’ reported level of educational attainment. Taken together, these results do not suggest that these PD subjects have experienced any signif

Table 3. Clinical test scores from the Parkinson’s disease subjects

| Measure | <i>n</i> | <i>M</i> | (<i>SD</i>) |
|---------------------------------------|----------|----------|---------------|
| WAIS–R subtests (%ile, age corrected) | | | |
| Information | 49 | 64.31 | (23.21) |
| Similarities | 47 | 64.58 | (25.37) |
| Digit Span | 48 | 57.10 | (23.10) |
| Block Design | 46 | 39.96 | (20.93) |
| Digit Symbol | 50 | 37.94 | (24.11) |

| | | | |
|--------------------------------------|----|--------|---------|
| WMS-R subtests (%ile, age corrected) | | | |
| Logical Memory I | 39 | 35.72 | (28.33) |
| Logical Memory II | 39 | 35.92 | (25.46) |
| Visual Reproduction I | 32 | 46.81 | (28.23) |
| Visual Reproduction II | 32 | 30.97 | (27.84) |
| CVLT Total Score (%ile) | | | |
| Percentile | 43 | 34.10 | (20.09) |
| BNT (Average correct) | 51 | 54.27 | (3.66) |
| COWA (average no. of words) | | | |
| FAS | 50 | 35.56 | (11.61) |
| Animals | 50 | 16.26 | (4.56) |
| Trails (time in seconds) | | | |
| A | 49 | 54.12 | (24.45) |
| B | 49 | 156.98 | (79.38) |
| Stroop (%iles, age corrected) | | | |
| Word | 44 | 26.68 | (19.35) |
| Color | 44 | 23.98 | (26.80) |
| Color-Word | 44 | 30.87 | (26.22) |
| Interference | 44 | 50.36 | (23.93) |

icant decline in general cognition. Further, it is noteworthy that the Parkinsonian's performances on tests requiring psychomotor output (e.g., Block Design, Digit Symbol, Trails A) were within the average range. Measures of executive function (e.g., Digit Symbol, Stroop, COWA, Trails A) were also within normal limits.

Procedures

Mental rotation ability was assessed with the Mental Rotations Test (e.g., Shepard, 1978; Shepard & Metzler, 1971) which can be administered either individually or in small groups of 2 to 4 volunteers (Vandenberg & Kuse, 1978). This paper-and-pencil test has 20 items with one target stimulus and four choices. Two of the four choices are correct, but are presented in different two-and three-dimensional planes, as if rotated to a different perspective. This test requires the participant to match the two correct choices to the target stimulus from four possible options. Because of the age range of these volunteers and possible difficulties of reduced vision, slight modifications were made to the test to facilitate performance. Test stimuli were enlarged by approximately 20% to enhance viewing (see Figure 1). Each example was presented on a separate page, and experimental test items were presented three per page. The participants responded on a separate answer sheet. Otherwise, test administration followed established procedures, including standardized instructions and a 10-min time limit (Vandenberg & Kuse, 1978). The dependent variable for this measure was the proportion of correct responses (number of correct items/total number of items attempted). Using a proportion correct score as the dependent variable was intended to correct for differences in psychomotor speed in test completion which may be a confound for individuals with Parkinson's disease.

RESULTS

The total correct scores and proportion correct scores for the men and women of each experimental group are presented in Table 4. Review of Table 4 indicates that the total correct scores of the male and female control subjects are consistent with that of previous research using normal adults of a similar age (Wilson et al., 1975).

The proportion correct data from Table 4 was subjected to a 2 (group) \times 2 (gender) ANCOVA, with age as

the covariate. Gender was included as an independent variable because a large male advantage has previously been found on this task (Linn & Petersen, 1985). Age was included as the covariate to account for possible age effects on this task (Wilson et al., 1975). Consistent with this previous research (Wilson et al., 1975), age was a significant factor in this analysis [$F(1, 102) = 4.98, p = .028$], and accounted for a small proportion of variance in this analysis, $R^2 = .01$. This analysis also yielded a significant main effect for group [$F(1, 102) = 12.13, p = .001$], indicating that Parkinson's subjects ($M = 55.94, SD = 12.30$) were less accurate on the MRT than control subjects ($M = 63.71, SD = 15.83$). A significant main effect for gender was also found [$F(1,102) = 18.55, p = .001$], indicating that men ($M = 64.81, SD = 16.03$) were more accurate on the MRT than women ($M = 54.73, SD = 11.06$).

The interaction between Group 3 Gender was also significant [$F(1, 102) = 5.21, p = .025$]. *Post-hoc* analyses with Bonferroni correction ($\alpha = .008$) on the age-corrected scores revealed that male control subjects were significantly more accurate than female control subjects [$t(54) = 4.51, p = .001$], whereas there was no difference in accuracy between male and female PD subjects. Male control subjects were also significantly more accurate than male PD subjects [$t(54) = 3.61, p = .001$], although there was no difference in accuracy between female control and PD subjects.

A series of supplementary analyses were conducted to assess the relationship between subject characteristics of the Parkinsonian subjects (e.g., symptom presentation, symptom severity, illness duration, medication status, level of depression) and their spatial orientation performance. To determine if symptom laterality was related to mental rotation performance in these PD subjects, a two-factor ANCOVA was conducted on the proportion correct scores, with laterality (e.g., right, left, bilateral) and gender as a between-subjects variable. Although there was no significant gender difference in MRT accuracy within the PD

Fig. 1. Mental Rotation Test example.

group, gender was included as a between subjects variable to account for any variability in performance that may interact with symptom laterality. Age was included as a covariate to account for age effects, and maintain consistency with the analysis described above. No significant effect was found for laterality [right $M = 56.10, SD = 13.90$; left $M = 58.90, SD = 14.29$; bilateral $M = 54.93, SD = 10.94$; $F(2, 42) = .07, p = .93$]. There was also no significant effect for age or gender, nor a significant interaction between Gender 3 Laterality.

To determine if the type of Parkinson's symptom (e.g., rigid-akinetic vs. tremulous vs. undifferentiated) exhibited by these subjects was associated with mental rotation ability, another ANCOVA was conducted on the MRT propor-

Table 4. Mental Rotation Test scores

tion correct scores, with predominant form of symptom and gender as the between subjects variables, and age as the covariate. This analysis revealed no significant difference in mental rotation accuracy associated with the PD symptom type [rigid-akinetic $M = 57.45, SD = 14.36$; tremulous $M = 58.48, SD = 7.90$; undifferentiated $M = 51.96, SD = 10.45$; $F(2,42) = 1.09, p = .35$]. Further, there was no main effect for age or gender, or an interaction between Gender 3 Predominant Symptom.

To assess the relationship between symptom severity and spatial orientation ability, a correlational analysis was conducted between the UPDRS score and the MRT accuracy score. To account for possible differences associated with sex, separate analyses were done for male and female PD subjects. Because the UPDRS score is based on a subjective ordinal scale, the proportion correct score was treated as rank order data for this analysis to allow comparison with the UPDRS score. The correlation between symptom severity and MRT accuracy for both men ($r = .5206$) and women ($r = .526$) was not significant.

| Controls | | PD | |
|----------|---------|-------|---------|
| Males | Females | Males | Females |

| MRT Score | <i>M</i> | (<i>SD</i>) | <i>M</i> | (<i>SD</i>) | <i>M</i> | (<i>SD</i>) | <i>M</i> | (<i>SD</i>) |
|--------------------|----------|---------------|----------|---------------|----------|---------------|----------|---------------|
| Total correct | 22.75 | (6.13) | 17.21 | (4.26) | 19.21 | (6.21) | 15.48 | (5.49) |
| Proportion correct | 71.45 | (15.76) | 55.97 | (11.73) | 58.16 | (13.55) | 53.23 | (10.24) |

To assess the relationship between the PD subjects' level of depression and spatial orientation performance, an ANCOVA was conducted on the proportion correct scores, with depression group (e.g., depressed, nondepressed) and gender as the between-subjects variables, and age as the covariate. Because of the small number of PD subjects reporting moderate to severe symptoms of depression, the data from these subjects was combined with the data of those reporting mild symptoms of depression to form one group. No significant difference in MRT accuracy were found associated with presence of symptoms of depression [nondepressed M 558.25, SD 59.76; depressed M 553.11, SD 512.81; $F(1, 37)$ 52.17, p 5.15]. There was also no significant effect for age or gender, or the interaction between Gender 3Depression.

To evaluate the association between medication status and mental rotation accuracy, the PD subjects were divided into two groups. Group 1 consisted of those 27 individuals taking additional medications (e.g., analgesics, anxiolytics, sleep aids, antidepressants) that might interfere with cognitive function plus an additional two subjects taking Parkinsonian medications with significant cognitive side effects (e.g., trihexyphenidyl). The remaining 22 subjects taking only Parkinsonian medications with no significant cognitive side effects comprised Group 2. The MRT accuracy scores were then subjected to a 2 (medication status) 32 (gender) ANCOVA, with age as the covariate. This analysis revealed no main effect for medication status [Group 1 M 55.42, SD 5 12.90; Group 2 M 56.62, SD 5 11.74; $F(1, 46)$ 5 0.02, p 5 .89]. There was also no significant effect for age or gender, or the interaction between Gender 3Medication Status.

Another correlational analysis was conducted between illness duration in years and MRT accuracy. Again, no significant relationship was found between disease duration and mental rotation accuracy for either men (r 52.08) or women (r 52.05).

A final series of correlational analyses was conducted between the MRT proportion correct score and the neuropsychological test scores. Again, separate analyses were conducted for male and female PD subjects to account for possible differences associated with sex. These results are presented in Table 5. Review of these findings indicates that, for men, mental rotation accuracy was significantly correlated with the Wechsler Adult Intelligence Scale–Revised Block Design subtest, which requires visual–spatial organization and problem-solving, and the Digit Symbol sub-test, which requires visual attention, scanning, and matching, as well as psychomotor speed and incidental learning. Mental rotation performance also correlated significantly with the speed of mental processing and response inhibition0

Table 5. Correlation between MRT accuracy score and neuropsychological test scores

PD subjects Measure Men Women

WAIS–R subtests Information Similarities Digit Span Block Design

Digit Symbol

WMS–R Subtests Logical Memory I Logical Memory II Visual Reproduction I

Visual Reproduction II

CVLT Total Score BNT (average correct) COWA (average)

FAS

Animals

Trails A B

Stroop Word Color Color-Word Interference .21 .31 .28 2.08 .36 .13 .56¹.10 .54²2.30

.33 2.70¹.28 2.65³.45 .16 .65².43
2.08 .18 .03 .35

.01 .12 .26 .35

2.37 .04

2.19 .21

.47⁴ 2.32 .53⁵ 2.14 .58⁶ .02 .01 .42

¹

¹ *p* 5.004 (2-tailed); ² *p* 5.003 (2-tailed); ³ *p* 5.008 (2-tailed); ⁴ *p* 5.017 (2-tailed); ⁵ *p* 5.006 (2-tailed); ⁶ *p* 5.002 (2-tailed).

cognitive set shifting on the Stroop Test, and delayed recall for visual-spatial information on the WMS-R. In contrast, women showed a significant inverse relationship between mental rotation accuracy and both immediate and delayed recall for verbal information on the WMS-R, indicating that higher mental rotation accuracy was associated with lower verbal memory. The correlations between the MRT proportion correct score and these cognitive test scores were further analyzed with Fisher *r*-to-*Z* transformation. Using Bonferroni correction (alpha 5.006, one-tailed), the difference in correlations between PD men and women were significant for the Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest (*z* 53.00, *p* 5.00135), Stroop Word Reading task (*z* 52.81, *p* 5.0026), the Wechsler Memory Scale-Revised Logical Memory tasks (Logical Memory I, *z* 5 4.39, *p* 5 .0001; Logical Memory II, *z* 5 3.43, *p* 5 .0003). The difference between correlations on the Stroop Color-Naming task was marginally significant (*z* 52.44, *p* 5 .0073). The difference between correlations on the WAIS-R Block Design subtest (*z* 51.70), Stroop Color-Word Reading task (*z* 52.14), and the Wechsler Memory Scale-Revised Visual Reproduction II (*z* 51.05) did not achieve significance.

The results of this study indicate that Parkinson's disease is associated with deficiencies in mental rotation in men. Specifically, men with PD demonstrated significantly lower scores on the Mental Rotations Test than men of similar age and education, whereas PD and control women performed at a similar low level. This floor effect indicates that the MRT is insensitive to visual-spatial deficits in PD females. Mental rotation performance in PD subjects was not affected by other factors, such as symptom laterality, symptom severity, symptom type, disease duration, medications, or mood. Because mental rotation is believed to be a basic component of visual-spatial ability (Bryden, 1982; Linn & Petersen, 1985; McGee, 1979; Stumpf & Eliot, 1999), these findings are consistent with previous research suggesting that PD is associated with diminished visual-spatial ability (Cummings & Huber, 1992; Growdon & Corkin, 1986; Stern & Mayeux, 1988). The reason men are impaired on the MRT is unknown, but there are several possible reasons.

Gender Differences

The finding of a significant interaction between group and the subject's gender may provide some insight into the mechanisms that underlie mental rotation deficits in PD. Men typically perform better than women on tests of mental rotation (Linn & Petersen, 1985; see also Halpern, 1992; Maccoby & Jacklin, 1974), consistent with our findings. The mechanisms underlying this sex difference are not entirely known, but mental rotation ability is typically mediated primarily by the right hemisphere (Corballis, 1997; see also Benton & Tranel, 1993; Bryden, 1982; Lezak, 1995). There is also evidence that there are sex differences in the lateralization of visual-spatial processing (Harris, 1978; Hiscock et al., 1995; Levy, 1974; Levy & Reid, 1978), and this enhanced male asymmetry might explain the male advantage in visual-spatial tasks (see Levy & Heller, 1992, for review). It has been suggested that there are two different strategies used when performing the MRT task: one might be more verbal categorical (top-bottom, left-right), and the other more non-verbal and continuous (Shepard & Cooper, 1982). This latter strategy, in which the entire stimulus is mentally moved as if in three-dimensional space (Shepard & Cooper, 1982), might be a more efficient process, and based on the superior performance by control men, they are more likely to use this process.

The MRT performance of women with PD was not significantly different from that of control women.

Notably, MRT accuracy of both control and PD women was not substantially above chance performance (50%, as defined by the overall probability of responding correctly to the test items; see Table 4), consistent with previous findings (see Wilson et al., 1975). That the men with PD did not perform statistically different from women in either group suggests that the men with PD lost the ability to use this mental rotation process.

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The correlational analyses support the postulate that the men with PD might perform mental rotations differently than the women with PD. Men showed a significant relationship between mental rotation ability and executive functions involving mental processing and psychomotor speed (e.g., Stroop Word Reading, WAIS-R Digit Symbol) that was different from women, although this finding was less than consistent (see Stroop Color Naming, Color-Word Naming, Interference, Trail Making Test). Whereas the WAIS-R Digit Symbol subtest does not appear to localize well (see Lezak, 1995, for discussion), a recent functional imaging study revealed bilateral anterior cingulate activation, as well as right parietal and left frontal operculum activation, during performance on the Stroop task (Brown et al., 1999). In contrast, women showed a significant inverse relationship between mental rotation ability and verbal memory. Thus, consistent with the “cognitive trade-off” hypothesis (see Levy & Heller, 1992, for review), women who rely on verbal memory and other verbal mediation processes are more likely to perform more poorly on the MRT. These findings are consistent with the supposition that normally men and women use different hemispherically mediated cognitive processes in performing visual-spatial tasks (Halpern, 1992; Hampson & Kimura, 1992; Levy & Heller, 1992). Additional research on these tasks with normal subjects will help elucidate the nature of these relationships.

Bradyphrenia

Slowed processing is not likely to explain the impaired MRT performance in the men with PD. Although there is some evidence of psychomotor slowing and difficulties with set-shifting in this sample of PD subjects (see Table 3, Trails B data), the majority of neuropsychological tests assessing psychomotor speed in the current study were within normal limits. Further, a proportion correct score was used as the dependent variable rather than the total correct score, thereby correcting for the total number of items each subject completed during the 10-min time limit of the test. This scoring approach was intended to control for the speed in which an individual subject completed the items on the test, and should have minimized the possible influence of psychomotor slowing. Consequently, mental rotation performance would be equated for each subject by taking into account the number of items completed.

Perception, Working Memory, and Imagery

While men with PD showed impaired mental rotation, deficient mental rotation performance can result from dysfunction in one of several possible components. In order for a person to compute a mental rotation, the individual must perceive the target stimulus and hold this perception in working memory as a mental image. The individual must then transform this mental image into a different perspective to learn if it matches each of the choices. With respect to visual perception, some visual disturbances have been reported in PD (Bodis-Wollner, 1990; Bodis-Wollner et al., 1987, 1991, 1993). However, these disturbances are thought to involve peripheral dysfunction in the retina rather than central cortical dysfunction, and these disturbances are responsive to dopaminergic treatment. Further, data from the neuropsychological assessment of our PD subjects do not indicate deficits in visual-spatial perception (Block Design) or working memory (WAIS-R Digit Span and Digit Symbol, WMS-R Logical Memory I and Visual Reproduction I) that could have accounted for the abnormal mental rotation performance of this sample of male PD subjects. Object imagery was not assessed in this sample, and a deficit in object imagery may account, in part, for the findings of this study. A deficit in imagery might be caused by the inability to

create and maintain an internal representation of the object, which is consistent with the findings of over-reliance on external environmental information in PD (Brown & Marsden, 1990). Other factors involved in mental rotation that could disrupt performance include the degree and/or dimension of the rotation (Corballis, 1997; Shepard, 1978; Shepard & Metzler, 1971), and these remain the topic of future research as well.

Neuropsychological Correlates of Mental Object Rotation

The anatomical localization of brain structures that subserve mental object rotation remains somewhat unclear. Although studies of individuals with lateralized brain damage generally indicate a right hemisphere advantage for mental rotation performance (Ditunno & Mann, 1990; Layman & Greene, 1988; Ratcliff, 1979; but see also Mehta et al., 1987), studies of mental rotation ability in normal subjects using tachistoscopic presentation procedures have been inconsistent in demonstrating a visual field advantage (Cohen & Polich, 1989; Corballis & McLaren, 1984; Corballis & Sergent, 1989; Fischer & Pelligrino, 1988; Jones & Anuza, 1982; Simion et al., 1980; Ueker & Obrzut, 1993; Van Strien & Bouma, 1990). Results from EEG studies are also inconsistent (Ornstein et al., 1980; Osaka, 1984). Functional imaging studies using magnetic resonance imaging have generally shown bilateral activation in both frontal and parietal regions (Cohen et al., 1996; Tagaris et al., 1997), although one study suggests that a hemispheric asymmetry exists that is dependent on whether the mental rotation is of an egocentric (left hemisphere) or extra-personal object-based (right hemisphere) transformation (Zacks et al., 1999). Studies of cerebral metabolism using positron emission tomography have generally found increased right hemisphere activation during performance of spatial orientation tasks (Deutsch et al., 1988; Gur et al., 1982; Harris et al., 2000). However, one study found no hemispheric asymmetry associated with mental rotation performance (Bulla-Hellwig et al., 1996), and another study found activity in left parietal region and basal ganglia during a mental rotation task involving alphanumeric stimuli (Alivisatos & Petrides, 1996).

Parkinson's disease is primarily a disorder of the basal ganglia, and these results indicate that the ability to perform mental rotations is a complex cognitive function that is dependent on intact function in the basal ganglia and their connections to the frontal lobes and parietal regions. Consequently, our results in the men are consistent with current theories of visual-spatial deficits in PD, which may be due to dysfunction in frontal-striatal circuits (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995), frontal-parietal systems (Cronin-Golomb & Braun, 1997), or parietal-striatal networks (Clower et al., 2002). Given these interconnections (see also Alexander et al., 1986, 1990; Middleton & Strick, 2000; Owen, 1997; Saint-Cyr, 2003, for reviews), dysfunction in one region can have a cascading effect that disrupts function in linked regions. However, it remains unclear if this deficit is primarily related to basal ganglia or cortical dysfunction. Most likely, however, this cognitive deficit is due to dysfunction within a distributed neural system that subserves visual-spatial perception, mental imagery, and mental manipulation of those images. Further research, however, is needed to elucidate the contribution of the different neuropsychological processes involved in spatial cognition, and to delineate the sex differences in the function of these respective processes.

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PREDICTING SUPRASPAN MEMORY IN PARKINSON'S DISEASE

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Running Head: Supraspan memory in PD

Abstract: Memory deficits, such as impaired word list-learning and recall, are commonly associated with Parkinson's disease (PD). However, the neuropsychological factors influencing these deficits have not been fully assessed. Using a supraspan word list-learning task, we found three variables that predicted memory function in our non-demented PD and control subjects. Long-delay free recall was predicted by: 5-trial total recall, short-delay free recall, and serial-order clustering. Further, cued-recognition/discrimination was predicted by: 5-trial total recall, short delay free recall, and short-delay free recall serial-order clustering. Accounting for these variables eliminated differences between groups on both delayed free recall and cued recognition. Because encoding, attention/concentration and information organization are typically associated with frontal-executive function, these results suggest that memory deficits in PD are associated with executive dysfunction often induced by frontal-striatal dysfunction.

Keywords: Memory, Parkinson's Disease, encoding, frontal-executive, sustained concentration, susceptibility to distraction

Patients with Parkinson's disease (PD) often complain about memory deficits and clinical research corroborates these patient reports. Deficits are most typically found on measures of supraspan memory, such as remembering word-lists (Auriacombe et al., 1993; Breen, 1993; Hart et al., 1992; Knoke et al., 1998; Massman et al., 1990; Taylor et al., 1986; Tweedy et al., 1982), although Filoteo et al. (1997) and Ivory et al. (1999) were unable to detect this deficit. Memory for verbal stories (e.g., Wechsler Memory Scale - Revised (WMS-R) Logical Memory; Wechsler, 1987) has also been shown to be impaired in PD (Blonder et al., 1989; Cooper et al., 1991; Hietanen & Teravainen, 1986; Sagar et al., 1991), but these findings have been inconsistent (Cronin-Golomb & Braun, 1997; Dubois et al., 1990; Sullivan et al., 1989; Taylor et al., 1986, 1990). Although somewhat variable, overall, these results suggest that individuals with PD have impaired verbal memory. This finding is particularly relevant because increased memory problems have been shown to predict the later development of dementia in PD (Woods & Troster, 2003).

The specific neuropsychological deficit that might account for this verbal memory deficit has not been fully determined. One possible guide to understanding these memory deficits might be to determine how the pathological processes associated with PD might induce cognitive dysfunction. PD is associated with degeneration of nigro-striatal pathways and, more specifically, dopamine depletion within these pathways. Given the extensive connections between the striatum and the cortex, particularly the frontal lobes (see Alexander et al., 1986, 1990 for reviews), this nigro-striatal dysfunction could also potentially induce frontal lobe dysfunction (Brown & Marsden, 1990, Taylor & Saint-Cyr, 1995). Additionally, Lewy bodies containing alpha-synuclein fibrils cannot only be found in the substantia nigra and ventral tegmental areas, but also in the frontal lobes of patients with PD (Kingsbury et al., 2004, see also Braak et al., 2003). Moreover, patients with PD, even in the absence of dementia, often demonstrate frontal lobe atrophy (Burton et al., 2004, see also de la Monte et al., 1989). Because executive skills are dependent on frontal lobe function (see Damasio & Anderson, 1993; Stuss & Benson, 1987 for reviews), patients with PD can exhibit deficits in executive skills, and several investigators have suggested that the frontal-executive deficits associated with PD might influence memory (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995).

Support for the postulate that the memory deficit associated with PD might be induced by executive dysfunction comes from the work of Bondi et al. (1993). These investigators found that statistically controlling for deficits in executive skills (e.g., standardized composite scores calculated from the Modified Wisconsin Card Sorting Test, California Sorting Test, verbal fluency measures, and a verbal temporal ordering task) through analysis of covariance eliminated deficits in memory, but statistically controlling for the memory and visual-spatial deficits did not alter the abnormal measures of executive function. Thus, their results suggest that frontal-executive dysfunction entirely accounted for the memory deficits associated with PD. The mechanism by which frontal-executive dysfunction induce memory deficits in patients with PD, however, remains unclear. Although some studies have found a correspondence between impaired working memory, a frontal lobe function, and deficits in long-term memory (Cooper et al., 1991; Higginson et al., 2003; Sullivan & Sagar, 1991), others have not found this relationship (Blonder et al., 1989; Dubois et al., 1990; Hietanen & Teravainen, 1986).

Alternatively, several investigators have suggested that retrieval deficits account for the memory problems seen in PD (Crosson, 1992; Levin et al., 1992). That is, information is adequately encoded and consolidated, but (effortful) retrieval of this (explicit) information is impaired. Information retrieval processes, particularly those involving the ability to remember the episode in which information is learned, also appears to depend on normal frontal lobe-executive functions (Manns et al., 1992; Moscovitch, 1992). This effortful retrieval postulate is consistent with previous findings that report PD patients who have frontal-executive dysfunction derive a benefit from cueing or recognition paradigms (e.g., Flowers et al, 1984; Taylor et al., 1986). However, Whittington et al. (2000), in a quantitative review of the literature, reported that, while the magnitude of a recognition memory deficit (e.g., effect size) is small in patients with PD, it is reliable, and that this recognition deficit might have not been reported previously because many earlier studies did not have sufficient statistical power (e.g., sample size) to adequately assess this effect. The presence of a recognition deficit suggests that the memory deficit associated with PD might not be entirely related to a retrieval deficit. Thus, the role of frontal lobe dysfunction in the memory loss associated with PD remains uncertain.

Notably, PD has also been associated with significant hippocampal atrophy (Bruck et al., 2004, Camicioli et al., 2003, Laakso et al., 1996, Riekkinen et al., 1998, Tam et al., 2005), and this hippocampal atrophy has been correlated with memory deficits (Bruck et al. 2004, Camicioli et al., Riekkinen et al., 1998). Thus, memory processes subserved by the hippocampus (e.g., consolidation) also appear to be affected in PD. Consequently, an alternative explanation for the memory problems seen in PD is that hippocampal dysfunction accounts for these cognitive difficulties.

This current study compares differences in long-term supraspan memory between individuals with PD and matched control subjects. In this exploratory study, using statistical modeling methods, we wanted to identify those variables that predict memory performance in PD, with the hope that the determination of these variables would allow us to specify those neuropsychological processes that underlie the memory problems in individuals with PD. As noted above, memory deficits associated with PD have been attributed to retrieval deficits induced by frontal-executive dysfunction or to the consolidation deficits induced by hippocampal dysfunction. Thus, we hypothesized that, if the frontal executive dysfunction associated with PD accounts for the memory problems seen in PD, variables reflecting frontal executive dysfunction would contribute to predicting memory performance, e.g., long-delay free recall. Further, we would expect that accounting for these frontal-executive processes would minimize any differences in performance between these groups on the delayed free recall and recognition recall conditions. In contrast, if frontal-executive dysfunction does not account for the memory problems associated with PD, we would expect there to be significant group differences even after accounting for the frontal-executive functions that contribute to memory. We would also expect there would continue to be a significant group difference in delayed free and recognition recall (e.g., significant interaction between group and memory retrieval task) after accounting for these other executive processes that contribute to memory formation.

METHODS

Subjects: Data from individuals with PD were collected through the University of Florida Neurology and Movement Disorder Clinics (28 men, 21 women). These neuropsychological assessments were conducted as part of the patients' regular clinical evaluation. Diagnosis of PD was based on a neurological evaluation, and symptom severity was rated using the Unified Parkinson's Disease Scale (UPDRS; Fahn & Elston, 1987). It should be noted that UPDRS data for one woman with PD was not available for this analysis. All PD volunteers were tested while on their prescribed medications. Family members and friends who accompanied the PD patients to the clinic, along with local volunteers, were recruited as control subjects (12 men, 17 women). All participants were screened with the Mini Mental State Exam (Folstein et al., 1975). To be included as a participant, a cut-off score of 27, which is higher than the usual cut-off of 24, was used to minimize the likelihood of a confounding neurodegenerative process other than PD being present (Malapani et al., 1994; Reed et al., 1997). All participants were native-English speakers and right handed according to self-report. Exclusionary criteria for all subjects included a history of other or concurrent neurological disorders, and a previous or current history of: a learning disability, brain trauma, a major psychiatric disorder, or substance abuse.

Apparatus and Procedures: The California Verbal Learning Test (CVLT; Delis et al., 1987) was administered following standardized procedures. Additional standardized neuropsychological testing was also conducted as part of the regular clinical evaluation for the PD patients, as well as part of a larger on-going research protocol. These measures included the Information and Digit Span subtests from the Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981), the Boston Naming Test (Kaplan et al., 1983), the Controlled Oral Word Association test (Spreen & Benton, 1977), the Stroop Color-Word Test (Golden, 1978), and the Trail Making Test (Reitan & Wolfson, 1985). Not all subjects received all of these neuropsychological tests. Because of this missing data, these neuropsychological test scores were not included in the regression analyses, but were used to better characterize these subjects.

ANALYSES

To accomplish our goals, we conducted a series of statistical analyses. In the first series of analyses, we simply examined for differences on the various CVLT indices between PD and control subjects. Subject characteristic variables (e.g., sex, age, education) known to affect cognition were included as covariates in order to isolate differences in memory function specifically associated with PD. In the second series of analyses, we subjected the CVLT long delayed recall score to a backward elimination regression analysis using CVLT indices of initial encoding, learning, sustained concentration and susceptibility to distraction, as well as subject demographic factors, as predictor variables. Although we recognized that there was a possibility of multicollinearity among the CVLT indices that could potentially bias the regression analysis, we intentionally included these specific variables because of their extensive use in the clinical assessment of memory function. For example, the Trial 1 score reflects initial encoding, whereas the Learning Slope reflects learning efficiency with repetition and the Five Trial Total score reflects total encoding efficiency. The Short-Delay Free Recall score typically reflects susceptibility to interference, whereas the Semantic and Serial Order Clustering scores reflect information organization strategies involved in learning. Consequently, these indices have interpretive value in better understanding the cognitive processes involved in memory, and these indices are thus frequently used clinically to explain the memory difficulties seen in our patients. We then repeated this analysis using the CVLT recognition recall index as the criterion. Finally, we examined for differences between the free recall and recognition recall measures, using the significant predictors identified in the regression analyses as covariates.

RESULTS

Subject demographic information is presented in Table 1. The age, education and MMSE data were subjected to separate analyses of variance, with Group and Sex as the between subjects variables. These analyses revealed that control subjects were significantly older than PD subjects, and men generally had more

years of education than women (14.70 ± 2.54 versus 13.57 ± 2.33 , $F(1,74) = 4.20$, $p = 0.044$). PD and control subjects performed similarly on the MMSE. Table 1 also includes information regarding symptom duration and severity of the PD subjects. These data were subjected to separate analyses of variance, with sex as the between subjects variable. Duration of illness was similar between men and women. However, women showed a trend for more Parkinsonian symptoms than men on the UPDRS.

Examination of the UPDRS data revealed that 16 PD subjects exhibited predominantly right-sided symptoms, 10 demonstrated predominantly left-sided symptoms, and 22 subject exhibited bilateral symptoms. Further examination of the UPDRS ratings indicated that 8 PD subjects exhibited tremor as their most prominent symptom, 24 exhibited rigidity and akinesia as their predominant symptom, and 16 subjects exhibited both tremor and rigid-akinesia (undifferentiated).

Scores from the cognitive measures are presented in Table 2. These data were subjected to separate analyses of covariance, with Group as the between subjects variable. Age, education, and sex were included as covariates to account for variance in these cognitive measures typically associated with these variables, thus isolating variance associated with group. These analyses revealed that PD and comparison subjects performed similarly on the Information and Digit Span subtests. Control subjects showed tendencies for better performance on the Boston Naming Test and Animal Naming task, but were otherwise similar on the letter fluency task (Controlled Oral Word Association Test). As expected, the individuals with PD exhibited deficits on measures of sequencing, mental processing speed, response inhibition, and set-shifting, as reflected on the Stroop and Trails tasks, relative to the comparison subjects. With respect to the contributions of the covariates, education showed a significant positive correlation with both the Information subtest Scale Score ($r = 0.54$, $p = 0.0001$) and the Boston Naming Test ($r = 0.33$, $p = 0.006$). The raw data suggested that age might show an inverse relationship with the Boston Naming Test ($r = -0.18$) and Animal Naming ($r = -0.19$), but these correlations did not achieve significance. With respect to the covariate Sex, men performed better on the WAIS-R Information subtest (12.4 ± 1.95 versus 10.8 ± 2.0 , $F(1,67) = 10.87$, $p = 0.002$), whereas women performed better on the Stroop Color-Word Naming task (50.9 ± 31.7 versus 33.0 ± 27.4 , $F(1,60) = 5.64$, $p =$

0.021), and showed a tendency for better performance on the Stroop Interference measure (59.1 ± 26.9 versus 48.7 ± 20.8 , $F(1,60) = 2.95$, $p = 0.091$).

Performance indices on the CVLT are presented in Table 3. With the exception of the primary outcome variables (Long-Delay Free Recall, Discrimination), these data were subjected to separate analyses of covariance, with Group (PD, Control) as the between subjects variable. Again, age, education, and sex were included as covariates to account for variance in memory performance typically associated with these variables, thereby isolating variance associated with Group. These analyses revealed that control subjects generally outperformed PD subjects across all CVLT memory indices except the Serial Order Clustering and Learning Slope indices. With respect to the influence of the covariates on memory, only the correlations between Education and CVLT Trial 1 ($r = 0.27$, $p = 0.019$), and between Education and the CVLT 5-trial total T-score ($r = 0.23$, $p = 0.048$) achieved significance. With the exception of the correlation with Serial Order Clustering, the remaining correlations with Education were positive. The correlations between Age and the designated CVLT indices did not achieve statistical significance. Women significantly outperformed men on all memory scores indicated ($p's \leq 0.034$). Also included in Table 3 is the amount of variance in the individual dependent variables predicted by the demographic covariates, as well as the additional, unique variance predicted by the subject group variable.

The primary outcome variables were subjected to a repeated measures ANCOVA, with retrieval measure (Long-Delay Free Recall, Discrimination) as the within subjects variable, group as the between subjects variable, and sex, age, and education as the covariates. The Long-Delay Free Recall score was converted to a percent recall score (e.g., number recalled divided by total number of items, i.e., 16) in order to make this score more comparable with the Discrimination (e.g., recognition) index. As expected, recognition performance was significantly greater than delayed-free recall, $F(1, 73) = 4.53$, $p = 0.04$. Consistent with the previous analyses, age ($F(1, 73) = 3.90$, $p = 0.052$) and education ($F(1, 73) = 3.67$, $p = 0.059$) had marginal effects as covariates, whereas sex ($F(1, 73) = 8.41$, $p = 0.005$) had a significant effect as a covariate. Moreover, the interaction between retrieval and sex was marginally significant, $F(1, 73) = 2.99$, $p = 0.088$. This marginal interaction indicates that women performed relatively better on delayed-free recall than men compared to their recognition

performance. As expected, this analysis revealed a significant group difference, $F(1, 73) = 11.56, p = 0.001$. Notably, the interaction between group and retrieval was also significant, $F(1, 73) = 5.00, p = 0.028$. Post-hoc analyses of this interaction, using Bonferroni correction for multiple comparisons ($\alpha = 0.01$), revealed significant differences between Control and PD subjects on both Delayed-Free Recall, ($t(75.64) = 3.38, p = 0.001$) and recognition ($t(76) = 3.04, p = 0.003$). Both Controls and PD subjects performed better on recognition than delayed-free recall (p 's < 0.0001). Notably, the magnitude of difference between the two groups was marginally greater for delayed-free recall (13.06 ± 17.99) than for recognition (5.74 ± 8.86), $t((75) = 2.31, p = 0.023$.

To identify those variables that are predictive of delayed verbal memory, a backward elimination regression was conducted using the CVLT Long Delay Free Recall score as the criterion, and several indices from the CVLT reflecting encoding, information organization, learning rate, and susceptibility to distractibility, along with subject demographic variables and group, as predictors. As discussed above, these CVLT indices were selected specifically because of their widespread use in the clinical assessment of memory function. Entry value for the equation was $p < 0.05$; the removal value was $p > 0.10$. See the regression model below.

Long Delay Free Recall = *1st Trial Recall + 5 Trial Total Recall + Semantic Clustering Total + Serial Order Clustering Total + Short Delay Free Recall + Short Delay Free Recall Semantic Clustering + Short Delay Free Recall Serial Order Clustering + 5 Trial Learning Slope + Age + Education + Sex + MMSE + Group (PD, Control)*

The initial full model was significant in predicting long delay free recall, Adjusted $R^2 = 0.745$, SEE = 1.57, $F(13,64) = 18.29, p = 0.0001$. As expected, there was some evidence of multicollinearity in the full model. Collinearity tolerances were low for both first trial recall (0.101) and 5-trial total recall (0.079), reflecting, in part, a significant correlation between these two variables ($r = 0.811, p = 0.0001$). Tolerances were marginal for short delay free recall (0.29) and learning slope (0.255), again reflecting, in part, a significant correlation between these variables ($r = 0.379, p = 0.0001$). All other tolerances were 0.513 or greater.

The final model derived in this analysis was nominally significant in predicting long delay free recall, Adjusted $R^2 = 0.769$, SEE = 1.49, $F(3,74) = 86.51$, $p = 0.0001$. This model yielded three variables in the equation after backward elimination (Table 4). These variables included: short delay free recall (SDFR), involving the ability to retain the word-list information, 5-trial total recall, involving learning of the word-list across five exposures, and serial order clustering, reflecting the use of rote order learning strategy. Collinearity tolerances for these three variables were 0.436 or greater.

To evaluate those variables predictive of recognition performance, another similar backward elimination regression analysis was conducted using the delayed discrimination index as the criterion. The initial full model in this analysis was significant in predicting recognition recall, Adjusted $R^2 = 0.523$, SEE = 6.57, $F(13,64) = 7.49$, $p = 0.0001$. Again, tolerances were low for trial 1 recall and 5-trial total recall, and marginal for short delay free recall and learning slope, reflecting multicollinearity amongst these predictors.

Following backward elimination, the final model was nominally significant in predicting the criterion, Adjusted $R^2 = 0.56$, SEE = 6.31, $F(3,74) = 33.71$, $p = 0.0001$. The final model included: short delay free recall, 5-trial total recall, and the short-delay free recall serial order clustering score (Table 5). Collinearity tolerances in the final model were 0.42 or greater.

To assess for differences between delayed free recall and recognition recall associated with PD, a repeated measures analysis of variance was conducted with retrieval task (e.g., delayed free recall versus recognition) as the within subjects variable and Group as the between subjects variable. Those variables identified as significantly predictive of long term memory function through regression analyses, 5-trial total learning, short-delay free recall, total serial order clustering, short-delay free recall serial order clustering, were included in the equation as covariates. For this analysis, the converted long-delayed free recall percent correct score (total number correct/total number possible) was used to allow for a more direct comparison with the recognition index. As before, a main effect was found for Retrieval Task (delayed free recall versus recognition recall), with the Discrimination index (89.36 ± 6.57) showing greater accuracy than Delayed Free Recall (58.27 ± 9.80), $F(1,72) = 81.62$, $p = 0.0001$. Consistent with the previous regression analyses, short-delay free recall contributed significantly as a covariate, $F(1,72) = 30.99$, $p = 0.0001$, as did 5-trial total recall, $F(1,72) = 24.15$, p

= 0.0001, and serial order clustering, $F(1,72) = 4.55$, $p = 0.036$. The interaction between short-delay free recall and recall task was also significant, $F(1,72) = 17.69$, $p = 0.0001$, indicating a differential effect in retrieval between delayed free recall ($B = 3.03$) and recognition recall ($B = 0.76$) associated with short-delay free recall ability. However, neither the main effect for Group, $F(1,72) = 0.25$, $p = 0.615$ nor the interaction between Group and Recall task, $F(1,72) = 0.000$, $p = 0.99$, achieved statistical significance.

Finally, a series of supplementary analyses were conducted to assess the influence of PD symptom characteristics on memory function. Laterality was operationally defined as exhibiting a preponderance of lateralized symptoms on the UPDRS, resulting in three subgroups: Right predominant, Left predominant, and Bilateral. Analyses of variance revealed no differences on either the long delayed free recall score ($F(2,45) = 0.09$, $p = 0.91$) or the discrimination index ($F(2,45) = 0.62$, $p = 0.54$). Symptom type was operationally defined as exhibiting a preponderance of specific PD symptoms on the UPDRS, resulting in three subgroups: Tremor predominant, Rigid-Akinetic predominant, and Undifferentiated. Analyses of variance found no differences on either long delayed free recall ($F(2,45) = 2.07$, $p = 0.14$) or discrimination ($F(2,45) = 0.23$, $p = 0.80$). Correlations between disease duration and the dependent variables yielded a significant inverse relationship between duration and the discrimination index, $r = -0.301$, $p = 0.036$. No significant correlation with symptom severity (UPDRS Total Score) was found for either long delay free recall ($r = 0.063$, $p = 0.67$) or discrimination ($r = 0.13$, $p = 0.38$). To assess for medication effects, the PD subjects were grouped according to those taking primarily Parkinsonian medications and those taking additional medications with other psychoactive properties (e.g., antidepressants, muscle relaxants). Independent samples t-tests revealed no difference between these two groups on either the long delayed free recall score ($t(38.82) = 1.045$, $p = 0.302$) or the discrimination index ($t(47) = 0.19$, $p = 0.85$). To examine for the effects of depressive symptomatology, the PD subjects were grouped according to their responses on the Geriatric Depression Scale, resulting in two groups: those reporting increased symptoms of depression and those not. Independent samples t-tests found no differences between these groups on either long term delayed free recall ($t(38) = 0.52$, $p = 0.604$) or the discrimination index ($t(38) = 1.22$, $p = 0.23$).

DISCUSSION

In general, the results of this study are consistent with the findings of several prior studies that showed delayed supraspan memory deficits in PD (Auriacombe et al., 1993; Breen, 1993; Buytenhuijs et al., 1994; Hart et al., 1992; Knoke et al., 1998; Massman et al., 1990; Taylor et al., 1986, 1990; Tweedy et al., 1982). These results are also consistent with the findings of Whittington et al. (2000) who showed that when patients with PD are compared to control subjects, the magnitude of difference in memory performance on recognition tasks is smaller than that of delayed free recall. However, recognition is nevertheless impaired. In addition, our results corroborate prior studies that found a significant influence of demographic factors, such as sex, age, and education, on memory (Delis et al., 1987). These data are also consistent with prior reports that patients with PD can have memory deficits despite intact mental status and language abilities (Taylor et al., 1990).

Two variables were consistently identified in predicting long-term supraspan memory in our group of PD and control subjects: 5-Trial Total Recall and Short-Delay Free Recall. Five-Trial Total Recall typically reflects encoding efficiency in learning with repetition. Short-Delay Free Recall typically reflects susceptibility to distraction, a measure of attention. Serial-Order clustering, during either the five learning trials or the short-delay free recall, also contributed to the prediction of long-term supraspan memory. Serial order clustering typically reflects rote order learning. The finding that serial order clustering was inversely related with long delay recall suggests that use of other forms of information organization such as semantic encoding might enhance encoding and consolidation, thereby influencing long delay recall. Together, these results suggest that measures reflecting encoding efficiency, distractibility/attention, and information organization can account for our subjects' long-term memory.

Other factors did not contribute to the differences in memory function between our control and PD subjects, despite preliminary findings of memory deficits associated with PD. In particular, potential differences between the PD and control subjects in the manner in which memory stores are accessed (free recall versus cued recognition) were eliminated after accounting for encoding efficiency, attention/distractibility, and information

organization. Thus, deficits in active information retrieval do not appear to explain the PD subjects' problems with memory.

Other factors known to affect memory (e.g., age, education and sex) also did not contribute to the equation in predicting long-term memory in this sample. Further, other manifestations of PD, such as symptom severity, symptom presentation, and medication status also did not appear to have a significant influence in memory performance.

The frontal lobes are known to be critical in the mediation of sustained attention-concentration by reducing the influence of distracting stimuli (Bauer et al., 1993; Stuss & Benson, 1987). The frontal lobes are also thought to be important in the organization of information (Binder et al., 1997; Demb et al., 1995; Demonet et al., 1992; MacLeod et al., 1998; Spitzer et al., 1998; Wise et al., 1991). Our results are consistent with clinical findings of frontal-executive deficits that have previously been reported in patients with PD despite intact mental status and language abilities (Taylor et al., 1990).

These results are also consistent with current theories that suggest that cognitive dysfunction in PD is related to disruption of frontal-striatal circuits as a consequence of the nigrostriatal dysfunction, which is characteristic of this disease (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995). However, we found no significant relationship between motor signs or medication status and memory performance. Thus, our results might be related to other disease processes that might injure the frontal lobes such as atrophy and/or the deposition of Lewy bodies (Kingsbury et al., 2004) in non-motor systems of the frontal lobe (Burton et al., 2004).

Our results corroborate those of Bondi et al. (1993) who, as mentioned earlier, demonstrated that statistically covarying for frontal-executive deficits eliminated differences in memory between control and PD subjects. In contrast, these investigators found that statistically covarying for memory function did not eliminate the differences in frontal-executive function between the PD and control subjects. Our study, however, also extend those of Bondi et al. by evaluating the possible contributions of the frontal-executive systems to memory functions such as encoding efficiency and information organization as well as attention-distractibility. Moreover, these results extend those in the current literature through the finding that, after taking into account encoding efficiency, attention/concentration, and information organization, the memory deficits associated with

PD do not appear to be associated with difficulties in active retrieval. Taken together, our current results indicate that the PD is associated with disruption in frontal-executive functions that subserve the efficient organization and allocation of attention, both of which are important in the encoding of new verbal information as well as subsequent consolidation and storage of this newly-learned information into long-term memory.

Although the current results argue against the supposition that PD can directly affect the strength of long-term memory consolidation or retrieval processes that leads to recall failures, this postulate cannot entirely be ruled out based on our study because methodological limitations constrain the interpretation of these data. In particular, the statistical analyses used in this study were exploratory in nature, and the data elimination procedures are susceptible to the effects of multicollinearity which can potentially bias the results and obfuscate variables that potentially contribute to the equation. Although multicollinearity tolerances were generally within acceptable limits, the possibility of collinearity amongst the predictor variables remains an issue that mandates a cautious interpretation of these data. Another limitation of our study might be sample size (78 subjects). Even larger sample sizes might be required to find complex interactions. A related limitation involves the sample selection such that these subjects were not matched explicitly on demographic variables known to influence long-term memory (e.g., age, education, and sex). Although these demographic variables did not contribute to the equation predicting memory performance, it is unclear how these factors would have contributed to the equation had the subject groups been more similar. A final limitation is the absence of additional neuropsychological measures of frontal-executive function, particularly for the control subjects. Inclusion of these variables in the analysis would have provided a better measure of frontal-executive function, as well as better assess the contribution of frontal-executive function to long-term memory.

In summary, these results suggest that, after accounting for measures of encoding efficiency, sustained concentration, and efficient information organization, differences in the group membership between PD and control subjects failed to predict long-term supraspan memory. Consistent with current theories on cognitive dysfunction in PD, these findings suggest that it is frontal executive neurological processes underlying information organization and encoding, and not the hippocampally-mediated information consolidation, storage, or retrieval, that account for the memory difficulties seen in PD. The results of this study also indicate that

future research should account for information encoding, sustained attention, and learning efficiency in the examination of memory function in PD.

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Table 1: Subject Demographics

| | Controls | | | PD | | | F | df | p |
|---------------------------|-------------------|-------------------|--------------|-------------------|-------------------|--------------|-------|------|-------|
| | Men | Women | Total | Men | Women | Total | | | |
| N | <i>12</i> | <i>17</i> | 29 | 28 | <i>21</i> | 49 | | | |
| Age | <i>70.2 (6.6)</i> | <i>68.1 (5.4)</i> | 69.01 (5.92) | <i>62.6 (8.1)</i> | <i>61.4 (9.8)</i> | 62.10 (8.77) | 14.62 | 1,74 | .0001 |
| Education ¹ | <i>14.5 (2.6)</i> | <i>13.9 (2.4)</i> | 14.17 (2.44) | <i>14.9 (2.6)</i> | <i>13.2 (1.6)</i> | 14.16 (2.37) | 0.11 | 1,74 | .75 |
| MMSE | <i>29.3 (1.0)</i> | <i>29.0 (0.9)</i> | 29.10 (0.90) | <i>29.0 (1.0)</i> | <i>28.7 (0.8)</i> | 28.87 (0.90) | 1.56 | 1,74 | .21 |
| Duration | | | | 10.8 (6.3) | 8.6 (5.2) | | 1.62 | 1,47 | .21 |
| UPDRS | | | | 27.9 (11.1) | 35.6 (15.8) | | 3.98 | 1,46 | .052 |
| Mean (standard deviation) | | | | | | | | | |

¹Significant effect for sex as an independent variable

Table 2: Cognitive Test Results

| Test (Dependent Variable) (Control N/PD N) | Controls | PD | F | df | p |
|--|---------------|----------------|-------|------|--------|
| WAIS-R Information (Standard Score) (21/48) ^{1,2} | 12.10 (1.97) | 11.48 (2.16) | 0.61 | 1,64 | 0.44 |
| WAIS-R Digit Span (Standard Score) (21/48) | 11.52 (2.73) | 10.69 (2.23) | 1.74 | 1,64 | 0.19 |
| Boston Naming (total) (21/49) ^{1,3} | 55.67 (3.31) | 54.59 (3.80) | 3.16 | 1,65 | 0.08 |
| COWA – Letter (total) (21/49) | 39.48 (11.69) | 36.14 (11.80) | 2.24 | 1,65 | 0.14 |
| COWA – Animal Naming (total) (21/49) ³ | 17.76 (4.48) | 16.47 (4.42) | 3.95 | 1,65 | 0.051 |
| Stroop Word Reading (percentile) (19/43) | 53.32 (17.22) | 26.27 (19.60) | 16.62 | 1,57 | 0.0001 |
| Stroop Color Naming (percentile) (19/43) | 54.26 (23.77) | 24.02 (27.48) | 12.74 | 1,57 | 0.001 |
| Stroop Color-Word Naming (percentile) (19/43) ² | 60.11 (28.30) | 32.26 (27.64) | 6.48 | 1,57 | 0.014 |
| Stroop Interference (percentile) (19/43) ² | 53.47 (24.45) | 53.19 (24.14) | 1.23 | 1,57 | 0.27 |
| Trails A (seconds) (21/48) | 28.38 (6.38) | 52.65 (24.72) | 14.75 | 1,64 | 0.0001 |
| Trails B (seconds) (21/48) | 75.29 (30.23) | 151.60 (76.76) | 18.75 | 1,64 | 0.0001 |
| Mean (standard deviation) | | | | | |

¹Significant effect for education²Significant effect for sex³Significant effect for age**Table 3: CVLT Performance**

| Controls | | | PD | | | F | df | p | R ² with | R ² change |
|----------|-------|-------|-----|-------|-------|---|----|---|---------------------|-----------------------|
| Men | Women | Total | Men | Women | Total | | | | | |

| N | 12 | 17 | 29 | 28 | 21 | 49 | | | | Demograph. | w/Group |
|-----------------------------|-------------|-------------|---------------|-------------|-------------|---------------|-------|------|-------|------------|---------|
| Trial 1 ¹ | 7.0 (1.9) | 7.1 (1.7) | 7.07 (1.73) | 5.4 (1.9) | 5.8 (1.9) | 5.59 (1.85) | 12.41 | 1,73 | .001 | 0.115 | 0.129 |
| Trial 2 ² | 9.7 (2.5) | 10.2 (1.6) | 10.00 (2.04) | 7.3 (2.4) | 8.7 (2.3) | 7.86 (2.47) | 16.64 | 1,73 | .0001 | 0.101 | 0.167 |
| Trial 3 ^{2,3} | 10.6 (2.2) | 11.1 (1.9) | 10.62 (2.04) | 8.5 (3.0) | 10.1 (2.5) | 9.20 (2.85) | 7.35 | 1,73 | .008 | 0.156 | 0.077 |
| Trial 4 ² | 11.0 (2.0) | 11.8 (2.4) | 11.48 (2.28) | 8.8 (3.2) | 10.5 (2.4) | 9.55 (3.01) | 10.21 | 1,73 | .002 | 0.138 | 0.106 |
| Trial 5 ^{1,2} | 11.7 (2.3) | 12.1 (2.1) | 11.90 (2.14) | 9.7 (3.2) | 11.3 (2.6) | 10.39 (2.98) | 6.62 | 1,73 | .012 | 0.124 | 0.073 |
| Total(raw) ^{1,2,3} | 49.3 (9.0) | 52.3 (7.4) | 51.07 (8.08) | 39.6 (12.3) | 46.4 (9.5) | 42.55 (11.61) | 14.39 | 1,73 | .0001 | 0.157 | 0.139 |
| Total(T-score) ¹ | 55.5 (10.0) | 50.4 (10.5) | 52.48 (10.44) | 40.1 (13.1) | 40.4 (11.8) | 40.20 (12.41) | 13.53 | 1,73 | .0001 | 0.134 | 0.135 |
| Sem.Clust. ^{1,2} | 1.7 (0.8) | 2.3 (0.9) | 2.03 (0.87) | 1.4 (0.7) | 1.7 (0.8) | 1.56 (0.77) | 5.58 | 1,73 | .021 | 0.135 | 0.061 |
| Ser.Clust. ^{1,2} | 2.5 (1.7) | 2.1 (1.4) | 2.30 (1.50) | 3.3 (2.0) | 2.0 (0.9) | 2.75 (1.71) | 0.27 | 1,73 | .61 | 0.148 | 0.003 |
| Slope | 1.1 (0.6) | 1.2 (0.5) | 1.11 (0.56) | 1.0 (0.6) | 1.3 (0.7) | 1.12 (0.62) | 0.00 | 1,73 | .96 | 0.043 | 0.000 |
| SDFR ^{2,3} | 9.1 (2.7) | 10.5 (2.2) | 9.90 (2.44) | 7.2 (3.3) | 8.8 (3.5) | 7.88 (3.43) | 10.89 | 1,73 | .002 | 0.112 | 0.115 |
| LDFR ² | 10.0 (2.2) | 11.1 (2.0) | 10.62 (2.11) | 7.8 (3.7) | 9.6 (2.6) | 8.53 (3.35) | 10.30 | 1,73 | .002 | 0.142 | 0.106 |
| DISCRIM ² | 90.2 (7.4) | 94.8 (4.4) | 92.86 (6.14) | 84.9 (12.7) | 90.1 (5.6) | 87.12 (10.52) | 8.42 | 1,73 | .005 | 0.129 | 0.090 |

Mean (standard deviation)

¹Significant effect for education as a covariate

²Significant effect for sex as a covariate

³Significant effect for age as a covariate

Table 4: Model Summary: LDFR

| | Standardized <i>B</i> | <i>t</i> | p |
|----------------------|-----------------------|----------|--------|
| SDFR | 0.515 | 6.21 | 0.0001 |
| 5 Trial Total Recall | 0.365 | 4.41 | 0.0001 |
| Serial Clustering | -0.122 | 2.00 | 0.049 |

Table 5: Model Summary: DISCRIM

| | Standardized <i>B</i> | <i>t</i> | p |
|-------------------------------------|-----------------------|----------|--------|
| 5 Trial Total Recall | 0.474 | 4.07 | 0.0001 |
| SDFR | 0.286 | 2.50 | 0.015 |
| Short Delay Serial Order Clustering | -0.178 | 2.27 | 0.026 |

Neuropsychological functioning in Parkinson's disease: The effects of asymmetrical symptom presentation and anxiety.

Paul S. Foster, Valeria Drago, Robert Rhodes, Gregory P. Crucian, and Kenneth M. Heilman

Many patients with Parkinson's disease (PD) experience asymmetrical motor symptoms as well as feelings of anxiety. The anxiety experienced by patients with PD appears to be related to a reduced influence of catecholamines on the limbic system and normal function of the frontal lobes is dependent on input from both the limbic system and basal ganglia. Thus, patients with PD who have heightened anxiety (HA) and predominantly right-sided symptoms might perform worse on measures of left frontal lobe function than patients with low anxiety (LA) and left sided symptoms. To test this hypothesis the Stroop Color-Word Test (SCWT) and the Trail Making Test (TMT) were administered to 16 Parkinson's disease patients with right-sided asymmetrical symptom presentation (RSP) and 14 with left-sided asymmetrical symptom presentation (LSP). The dependent measure consisted of percentile scores on these tests. Patients were equivalent in terms of duration of illness, MMSE score, and estimated IQ. The results indicated a significant Group (High versus Low Anxiety) x Symptom (Left versus Right) interaction for Color-Word performance on the SCWT (SCWT-CW) as well as performance on Part B of the TMT (TMTB). Subsequent analyses indicated that the HA-RSP group performed significantly worse (TMTB: $M = 12.25$; SCWT-CW: $M = 12.78$) than the HA-LSP group (TMTB: $M = 48.50$; SCWT-CW: $M = 42.71$) as well as the LA-RSP group (TMTB: $M = 38.57$; SCWT-CW: $M = 50.71$). Thus, the combination of high anxiety and right-sided Parkinsonian signs appear to be associated with deficits in left frontal lobe functions.

Words = 248

Relationships between verbal and nonverbal memory and the laterality of Parkinsonian signs.

Paul S. Foster, Valeria Drago, Robert Rhodes, Gregory P. Crucian, and Kenneth M. Heilman

Research investigating neuropsychological differences between left versus right asymmetrical symptom presentation in Parkinson's disease has yielded mixed findings. However, many of these investigations have used tests that are not well suited for investigating lateralized neuropsychological functions and have not employed methods using a factorial design. Studies of patients with temporal lobectomy have revealed that left temporal lobectomy impairs verbal and right visuospatial memory. The present investigation sought to investigate material specific memory impairments in Parkinson's patients with predominantly left-sided (LSP) or right-sided (RSP) signs. It was hypothesized that LSP patients (12 subjects) would evidence greater nonverbal memory impairment and that RSP patients (10 subjects) would evidence greater verbal memory impairment. Verbal memory was assessed using percentile scores from the Logical Memory (LM) subtest of the WMS-III and the Hopkins Verbal Learning Test (HVLT). Nonverbal memory was assessed using the Faces subtest of the WMS-III and the Brief Visuo-Spatial Memory Test (BVMt). The result indicated a significant Group (LSP versus RSP) x Memory (Verbal versus Nonverbal) x Time (Immediate Recall versus Delayed Recall) interaction. Subsequent analyses indicated significant improvement in verbal recall for the LSP group (LM: Immediate Recall $M = 32.17$, Delayed Recall $M = 49.50$) and significant improvement in nonverbal recall for the RSP group (Faces: Immediate Recall $M = 37.30$, Delayed Recall $M = 56.10$). No other comparisons were statistically significant. Catecholamines are critical for the limbic (hippocampal)-cortical interactions needed for memory consolidation. These results suggests that an asymmetrical reduction of these neurotransmitters selectively influence material specific memories.

Words = 250

Learning in Alzheimer's and Parkinson's disease.

Paul S. Foster, Robert D. Rhodes, Brianna Lohse, Brian Shenal, Gregory P. Crucian, and Kenneth M. Heilman

Classical measures of learning have utilized a difference score obtained from subtracting the number of words recalled on the first trial of a supra-span word list from the best performance of the last two trials. However, this measure fails to capture total learning capacity across trials. Further, measures of total recall confound working memory with learning-declarative memory. Hence, a new measure of learning was created by multiplying the traditional learning score by the total recall across all learning trials. We analyzed learning on the Hopkins Verbal Learning Test (HVLT) using the traditional and the new learning score in a group of Alzheimer's (AD) and Parkinson's (PD) patients. We found that, using the traditional score, performance on the HVLT for 43 patients with AD ($M = 2.19$) was similar to that of normative participants ($M = 3.25$), with both groups demonstrating traditional learning curves. We also found that the traditional learning score for 37 AD patients ($M = 2.24$) was not significantly different than the score obtain from a sample of 24 PD patients ($M = 2.71$) with similar age and education. Using the new learning score, however, a large difference was obtained between the AD patients ($M = 22.95$) and the normative sample ($M = 85.70$), as well as between the groups of AD ($M = 23.41$) and PD patients ($M = 52.75$). These results suggest that this new learning measure might better discriminate patients with impaired learning, than does either the total score or the difference score.

Words = 248

The effects of mental processing speed on immediate and delayed recognition in Parkinson's disease.

Paul S. Foster, Valeria Drago, Robert Rhodes, Gregory P. Crucian, and Kenneth M. Heilman

Parkinson's disease (PD) patients might exhibit an improvement in memory over time, with greater delayed than immediate recall. They also often exhibit deficits with mental processing speed (bradyphrenia), as assessed by performance on the Color Naming portion of the Stroop Color-Word Task (CN-SCWT). We sought to examine whether bradyphrenia is related to the delay recall memory gains associated with PD. Based on this bradyphrenia postulate we predicted that PD patients with lower scores on the CN-SCWT (LCN group) would evidence significant increases in recognition from the immediate to delayed trials on the Faces subtest of the WMS-III and that PD patients with higher scores on the CN-SCWT (HCN group) would evidence stability across trials. The Faces subtest was administered to 23 LCN PD patients and to 24 HCN PD patients. Their percentile scores served as the dependent measure. The results indicated a significant interaction between Group (LCN versus HCN) and Time (Immediate versus Delayed). Subsequent multiple comparisons indicated that whereas the LCN group evidenced a significant improvement in recognition of pictures of faces from the immediate ($M = 33.78$) to the delayed ($M = 44.39$) recognition conditions, the HCN group evidenced no significant difference (Immediate: $M = 69.29$, Delayed: $M = 64.08$). Further, the LCN group performed significantly lower than the HCN group at both the Immediate and Delayed recognition trials. Thus, these results support the notion that bradyphrenia might partially explain the improvements in delayed in some PD patients, but also suggest that bradyphrenia might overall impair memory.

Words = 248

Visual-spatial disembedding in Parkinson's Disease.

Crucian, G.P., Armaghani, S.J., Armaghani, A., Foster, P.S., Burks, D.W., Drago, V., Rhondes, R.D., Okun, M.S., Fernandez, H.H., & Heilman, K.M.

Parkinson's Disease (PD) is often associated with deficits on visual-spatial tasks (Cummings & Huber, 1992, Growdon & Corkin, 1986, Stern & Mayeux, 1986). However, a meta-analysis of this literature (Waterfall & Crowe, 1995) suggests that visual-spatial deficits in PD are not universal because deficits are typically seen on multifactorial tasks (e.g., Raven's Progressive Matrices) but not more unifactorial measures of visual-spatial ability (e.g., Judgment of Line Orientation, Embedded Figures Test). Waterfall and Crowe identify several issues that potentially confound data interpretation in this research area, including subject characteristics (e.g., age, sex, education), illness duration, current disability level, the presence of emotional depression, the current medication levels, and the presence of dementia. The goal of this study was to assess visual-spatial ability in individuals with PD using a standardized test of visual closure and disembedding. 27 non-demented individuals with PD (17 men) and 19 healthy adults (8 men) similar in age and education participated in this study as part of a larger research protocol. Visual-spatial disembedding was assessed with the Hidden Patterns Test (Ekstrom et al., 1976). After statistically accounting for age, education, and sex, PD subjects were significantly less accurate in disembedding than controls, with rigid-akinetic PD subjects exhibiting greater difficulties. Notably, disembedding performance in these PD subjects was not associated with symptom laterality, illness duration, mood status, or medication status. These results corroborate previous findings of visual-spatial deficits in PD, reflecting perceptual deficits associated with right hemisphere dysfunction, and potentially involving narrowed focal attention (Barrett et al., 2001).

Running head: EMOTION WORD RATINGS IN PARKINSON'S.

Abnormal Emotional Word Ratings in Parkinson's Disease.

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Abstract

Blunted facial expressions and diminished emotional prosody associated with Parkinson's disease (PD) could be attributed to motor rigidity / akinesia. Although impaired recognition of emotional faces and prosody in PD suggests emotional dysfunction is not entirely motor-efferent, comprehension might depend upon imitation with motor feedback. Thus, to learn if PD patients have an emotional conceptual defect they rated the emotional connotations of words. Compared to control participants their valence and arousal ratings were blunted, but not their ratings of the control expense words. These blunted emotion ratings suggest that patients with PD have a degradation of their emotional conceptual-semantic system.

Key Words: Parkinson's disease, emotional expressions; emotional comprehension, affective semantics

Abnormal Emotional Word Ratings in Parkinson's Disease.

Parkinson's disease (PD) is a degenerative disorder that is associated with motor deficits, including bradykinesia, rigidity and tremor. Patients with PD can also have executive dysfunction, cognitive deficits and impairments of emotional behaviors (Cummings & Benson, 1992). For example, patients with PD typically demonstrate blunted facial expressions resulting in a mask-like, expressionless face. In addition, their speech is often aprosodic with an inability to express emotional prosody because they have restricted variations of fundamental frequency and amplitude (Heilman *et al.*, 2000). While some investigators attribute these emotion expressive deficits associated with PD to their motor deficits, such as motor rigidity and /or akinesia (Duffy, 1995), others have argued for deficits in the mediation of emotions (Benke *et al.*, 1998; Jacobs *et al.*, 1995; Smith *et al.*, 1996). The observations that patients with PD have additional impairments in the recognition of prosody and emotional faces (e.g. Dujardin *et al.*, 2004; Jacobs *et al.*, 1995; Sprengelmeyer *et al.*, 2003; Yip *et al.*, 2003) suggest that their emotion defects cannot be entirely explained by primary motor deficits, but that these patients have a more general dysfunction of the systems that mediate emotions (Benke *et al.*, 1998; Jacobs *et al.*, 1995). Some investigators, however, have found no impairment in the ability of patients with PD to comprehend, discriminate and rate emotional faces (Adolphs *et al.*, 1998; Pell & Leonard, 2005). Therefore, results are currently mixed regarding processing of emotional facial expressions.

Even if patients with PD have problems comprehending emotional prosody and facial expressions, these deficits might still be related to their motor deficits. It is possible that the comprehension of emotional facial expressions and prosody is dependent upon covert imitation with motor feedback. Thus, it remains unclear if patients with PD have an emotional processing deficit that is independent of their motor deficits.

Patients with PD who are not demented have problems with verbal or written expression or comprehension. Thus, a possible alternative means of investigating the Parkinsonian emotional deficit hypothesis is to study PD patients' ability to express and comprehend emotions when using propositional language (e.g., words and sentences).

Kan *et al.* (2002) investigated the ability of PD patients' ability to process emotions by presenting with written asking them to select the emotion most closely associated with these sentences (happiness, sadness, anger,

fear, surprise, or disgust). The investigators also assessed these patients ability to comprehend emotional facial expressions. Although those with PD showed deficits in recognizing fear and disgust in facial expressions, no impairments were seen in their recognition of written verbal stimuli.

It is possible that Kan *et al.* (2002) failed to find impairments in the emotional comprehension of written propositional language because their test was insensitive. Rather than classifying emotions, judging the emotional intensity of written stimuli may be a more sensitive method for detecting emotional processing impairments. If the intensity ratings of the emotionality associated with words is blunted in PD, but the ratings of non-emotional (expense) words rating is not impaired, it would suggest that patients with PD have a degradation of their emotional-semantic networks. Thus, in this study patients with PD, as well as control participants, rated the emotional connotations of written words representing a variety of emotion intensities. We hypothesized that the ratings of those with PD would be blunted for emotional judgments but within normal limits for judgment of non-emotional words.

Method

Participants: Eight experimental subjects with severe Parkinson's disease (PD) took part in this experiment. The demographic and psychometric data for the PD participants can be found in Table 1. All had severe PD as noted on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). All the PD participants were on dopaminergic (anti-Parkinsonian) medications. None of the participants reported a prior history of stroke, or other neurological or psychiatric disorders, and all were within normal cognitive levels in a dementia screening test. Participants in both groups were recruited from the University of Florida and all aspects of the study were approved by the Institutional Review Board of the University of Florida. Fifteen participants of similar ages as the PD group, but without neurological illness, served as a comparison group.

<PLEASE INSERT TABLE 1 AROUND HERE>

Apparatus: A set of 164 emotion words was selected from stimuli available from Lang *et al.* (1992, unpublished data) as well as additional nouns that were designed to elicit different emotions (e.g., waterfall, tornado). A set of 66 non-emotional items (nouns) that could be purchased at stores was also developed. Items were chosen to reflect a range of costs, from inexpensive (e.g. crayon) to expensive (e.g. pearl). Our healthy comparison group who provided emotional ratings for these 164 emotional words and expense ratings for the 66 nouns. Based on the range of ratings given in the normative sample, we selected 58 words for emotion ratings and 30 words for expense ratings to be used as stimuli in this study. In the emotion word set, 27 words have a positive valence (average rating of >6.5, e.g., diamond, serene), eight words were of neutral valence (average ratings between 3.5-6.5, e.g., pencil, startled), and 23 words were negatively valenced (average rating <3.5, e.g., lonely, fire). In the emotion word set, 18 words were rated as high arousal (average ratings >7.0, e.g., surprise, kiss), 20 words were rated as neutral (average ratings between 5.0-7.0; peach, confident), and 20 words were rated as low arousal (average ratings <5.0; e.g., lonely, map). Among the 30 expense related words, eleven were high expense words (average ratings >6.5, e.g. gold, car), nine mid expense words (average ratings between 3.5-6.5, e.g. suit, television), and ten were low expense words (average ratings <3.5, e.g. pencil, comb). The

distribution of arousal ratings varied around a higher mean than was observed in the expense or valence ratings; consequently, cut points for “low,” “mid,” and “high” arousal were adjusted upwards accordingly.

Procedures: The experimental task required participants to make ratings about the emotional valence and arousal associated with a set of written words. In the control condition, participants made ratings about the expense associated with a series of written words. Participants were shown 58 emotion related words and 30 expense related words one at a time. Words were presented on cards placed in front of the participant. In both the emotion and expense word tasks, participants were given as much time as necessary (usually 2-5 seconds) to rate each word by placing a mark on a visual Likert scale patterned after SAM (Self-assessment mannequin; Lang *et al.*, 2001) and varying from 1 to 9. For emotional valence, or pleasure, the scale progressed from 1 = very unhappy to 9 = very happy, with 5 being neutral. Participants were asked to rate whether the word for them personally was associated with feeling happy or unhappy. For grading arousal the scale ranged from 1=calm to 9=excited. Participants were asked to think of whether the feeling associated with that word “got them going” inside, ranging from very calm to very excited. The expense scale progressed from 1=cheap to 5=moderate to 9=expensive. Participants were asked to rate how expensive that item tended to be.

Participants were tested individually in a quiet room. Following a brief practice period, participants made all their ratings for the full set of words for in one dimension (i.e., valence, arousal, or expense) before rating the words for the next dimension. The order of the three dimensions was systematically varied across participants, and the order of words was presented randomly across participants. All ratings were completed within a 30 minute session.

Ratings given by participants for high, mid, and low rated words were examined separately in each of the three categories; emotion word valence, emotion word arousal, and control expense words. Ratings were compared between the two participant groups with 2 (group: PD and Comparison) x 3 (high, mid, low) ANOVAs.

Results

Mean word ratings and standard deviations for both participant groups are shown in Figure 1. For all three categories (valence, arousal, expense) there was a significant main group effect for ratings, and a significant interaction between participant group and ratings (see Table 2). For valence ratings of emotion words, post-hoc comparisons showed those with Parkinson's disease rated the positive words significantly lower on valence than the comparison group, and rated negative words significantly higher on valence. For arousal ratings post-hoc comparisons showed that those with PD rated the low arousal / calm words as significantly more arousing than the comparison group, though there was no difference for the high arousal words.

<PLEASE INSERT TABLE 2 AROUND HERE>

<PLEASE INSERT FIGURE 1 AROUND HERE>

To learn if the PD participants had a propensity to restrict their ratings overall, independent of content of the words, the PD and control participants also rated the non-emotional expense words. Post-hoc comparisons showed that those with PD rated both the high and mid expense words as significantly higher in expense than the control participants, indicating that the PD participants did not have an overall propensity to rate words in the middle of the scale and away from the extreme ends of the scale.

Discussion

Our results demonstrate that the participants with PD, when compared with the control participants, gave blunted ratings for the emotional, but not expense words. The valence ratings were blunted at both extremes, lower for words associated with positive emotions and higher for words associated with negative emotions. Arousal ratings were higher for words at the low arousal 'calm' end of the scale. The valence and arousal scales differ however, as low arousal results in a low score but low or neutral valence results in a mid-range score.

As mentioned, some previous studies have found that people with PD are impaired at expressing emotions (faces and prosody), and at recognizing and discriminating emotional expressions. These results are compatible with a motor disorder that impairs both expression and imitation-feedback as well as a deeper emotional conceptual-semantic defect. Our results, however, would appear to support the postulate that PD is associated with an impairment of the emotional conceptual-semantic networks. However, the possibility remains that a more general deficit in semantic processing or imagery could also be present.

Our findings contrast with those of Adolphs *et al.* (1998) who found that people with PD could comprehend emotional expression, suggesting that emotional conceptual networks are intact in people with PD. There are several possible explanations of the dissociation between the results of the Adolphs *et al.*'s study and our own. One possibility is that there are at least two emotional conceptual-semantic systems, one verbal and the other non-verbal, and in people with PD the former system is more impaired than the latter system. It is also possible that the emotions associated with words are less transparent than those associated with faces or prosody, and thus language-based stimuli are more sensitive to conceptual-semantic deficits.

These explanations, however, cannot explain why our results are also different from those of Kan *et al.* (2002) whose participants with PD showed no impairments in recognizing written stimuli. One of the methodological differences between our study and the studies of Kan *et al.* (2002), as well as that of Adolphs *et al.* (1998), is that their studies required recognition-discrimination of different emotions (classification) and ours required judgments of intensity which may be more sensitive to the emotion word processing deficits of PD.

The classification of emotional stimuli might be accomplished by having these stimuli access emotional iconic or echoic representations (Bowers *et al.*, 1991) and then verbal-lexical semantic representations. In contrast, when asked to rate the valence or arousal of a word, a person might have to activate the emotional systems that normally mediate that emotion. Patients with PD often show evidence of frontal lobe dysfunction and the frontal lobes seem to play an important part in the representation of emotional valence (Heilman, 1994; Lane *et al.*, 1994). In addition, the amygdala plays a critical role in the mediation of some emotions, particularly negative emotions with high arousal such as fear. Evidence using functional magnetic resonance imaging (fMRI) suggests that people with PD demonstrated a reduced amygdala response during perceptual processing of fearful and angry faces. This was influenced by dopaminergic modulation so that when participants were on-drug they

showed a partial restoration of the amygdala response compared to off-drug (Tessitore *et al.*, 2002). These studies suggest that the impairments of the frontal–basal-ganglionic and limbic systems that are associated with PD (Jacobs *et al.*, 1997) might be the critical factors that induce emotional impairments (blunting) observed in this study. Future studies will have to test the hypothesis that the networks that mediate the grading of emotional valence and arousal are different from than those that are important in the classification-discrimination of emotions.

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Table 1.

Parkinson's disease patients' demographic and psychometric data.

| Age | Years of Education | Sex | Years with PD | Handedness | MMSE | UPDRS |
|-----|--------------------|--------|-----------------|------------|------|-----------------|
| 7 | 12 | Female | -- ^a | Right | 29 | 46 |
| 7 | 20 | Male | 14 | Right | 29 | 41 ^b |
| 6 | 14 | Female | 5 | Right | 20 | 36 |
| 7 | 12 | Male | 7 | Right | 29 | 41 |
| 7 | 12 | Female | 7 | Right | 28 | 34 |
| 5 | 9 | Male | 11 | Left | 28 | 32 |
| 4 | >20 | Male | 8 | Right | 30 | 14 |
| 4 | 13 | Female | 7 | Right | 30 | 39 |

Note. ^a. not noted in chart; ^b. motor exam reported only for the post right pallidotomy test session

MMSE: Mini Mental State Examination Score (Folstein *et al.*, 1975)

UPDRS: Unified Parkinson's Disease Rating Scale, Part III Motor Exam (Fahn & Elton, 1987).

Table 2.

Means, standard deviations, and statistical comparisons of ratings for emotion and expense words between those with Parkinson's disease and the comparison group.

| | PD mean (SD) | Comparison mean (SD) | PD vs. Comparison | | | |
|------------------|-----------------|-------------------------|-----------------------|-------|-----------------|------|
| Emotion Valence | | | Main effect group | | Group X Valence | |
| | | | F | p | F | p |
| | | | 0.07 (df=1) | .70 | 7.22 (df=2) | .002 |
| | | | t | | | p |
| High (n=27) | 6.95 (1.17) | 7.48 (.62) | 2.38 (df=26) PD<Comp. | | | .025 |
| Mid (n=8) | 4.66 (.87) | 4.83 (.95) | .98 (df=7) PD=Comp. | | | .36 |
| Low (n=23) | 2.97 (1.27) | 2.40 (.55) | 2.78 (df=22) PD>Comp. | | | .01 |
| Emotion Arousal | | | Main effect group | | Group x Arousal | |
| | | | F | p | F | p |
| | | | 4.44 (df=1) | .04 | 4.46 (df=2) | .02 |
| | | | t | | | p |
| High (n=20) | 7.43 (.54) | 7.44 (.36) | .09 (df=19) PD=Comp. | | | .93 |
| Mid (n=18) | 5.98 (.99) | 5.96 (.49) | .09 (df=17) PD=Comp. | | | .94 |
| Low (n=20) | 5.06 (1.04) | 4.40 (.47) | 3.38 (df=19) PD>Comp. | | | .003 |
| Control Expense | | | Main effect group | | Group x Expense | |
| | | | F | p | F | p |
| | | | 35.89 (df=1) | .0005 | 4.58 (df=2) | .02 |
| | | | t | | | p |
| Expensive (n=11) | 8.42 (.58) | 7.51 (.92) | 4.66 (df=10) PD>Comp. | | | .001 |
| Moderate (n=9) | 6.22 (1.51) | 4.84 (.79) | 3.95 (df=8) PD>Comp. | | | .004 |
| Cheap (n=10) | 1.92 (.54) | 1.62 (.40) | 1.47 (df=9) PD=Comp. | | | .18 |

Figure 1.

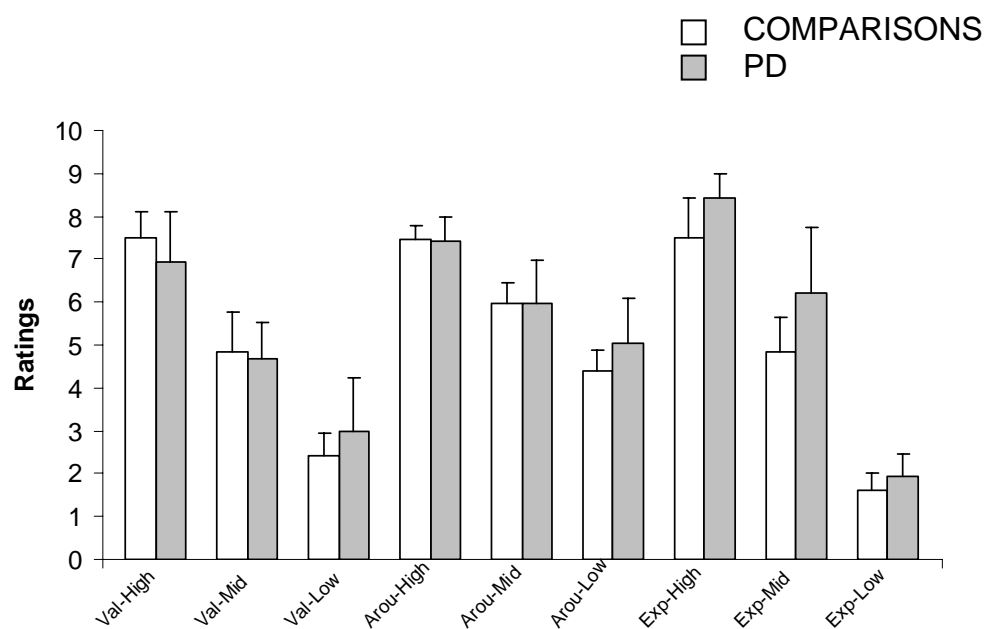


Figure 1.

Mean ratings for emotion (valence and arousal) and expense words.